Background Information

For

Bone, Reproductive and Urologic Drugs Advisory Committee

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Biologics License Application for Romosozumab

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
AFF	atypical femoral fractures
ApoE	Apolipoprotein E
ARR	absolute risk reduction
AUC	area under the curve
BLA	Biologics License Application
BMD	bone mineral density
BMI	body mass index
CKD	chronic kidney disease
C_{max}	maximum serum concentration
CT	computed tomography
(s)CTX	(serum) collagen type 1 C-telopeptide
CV	cardiovascular
CV SAEs	cardiovascular serious adverse events
CYP	cytochrome P450
DCRI	Duke Clinical Research Institute
FDA	Food and Drug Administration
FEA	finite element analysis
FRAX	fracture risk assessment tool
HR	hazard ratio
HCPCS	Healthcare Common Procedure Coding System
IgG2	immunoglobulin G2
IPCW	inverse probability of censoring weights
iPTH	intact parathyroid hormone
IPTW	Inverse probability of treatment weights
KO	knockout
MACE	Major cardiac adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDC	National Drug Codes
NOF	National Osteoporosis Foundation
ONJ	osteonecrosis of the jaw
OVX	ovariectomized
PBRER	Periodic Benefit Risk Evaluation Report
PD	pharmacodynamic(s)

Abbreviation or Term	Definition/Explanation
P1NP	procollagen type 1 N-terminal propeptide
PK	pharmacokinetic
PMO	postmenopausal osteoporosis
PTH	parathyroid hormone
QCT	quantitative computed tomography
SC	subcutaneous(ly)
SNP	single nucleotide polymorphism
TIMI	Thrombolysis In Myocardial Infarction
US	United States
Wnt	wingless-related integration site

1. Executive Summary

Introduction:
Romosozumab is a humanized monoclonal antibody (immunoglobulin G_2) that inhibits sclerostin, thus having the dual protective action of promoting bone formation and decreasing bone resorption.

Amgen is seeking approval of romosozumab for the treatment of women with postmenopausal osteoporosis (PMO) at high risk for fracture. The intended dosing is sequential therapy with romosozumab 210 mg every month for one year, followed by antiresorptive therapy. This dosing paradigm was evaluated in all phase 3 studies.

The Biologics License Application (BLA) included data from approximately 14 000 subjects in the romosozumab clinical program. This document summarizes key information in support of the proposed indication for the Bone, Reproductive and Urologic Drugs Advisory Committee.

Unmet Medical Need:
Osteoporosis is a well-recognized public health issue that is on the rise due to the aging population in the United States (US) and other countries. Fracture is the single most important sequela of osteoporosis. In the US, osteoporosis-related fractures occur in about 1 in 2 Caucasian women who reach 50 years of age (NOF, 2018).

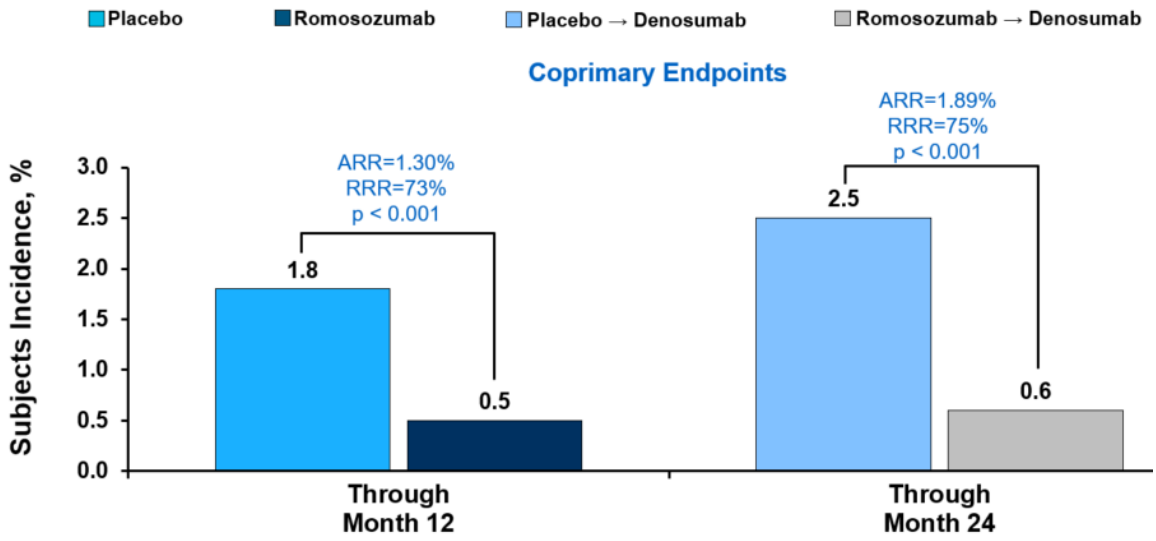
Among patients who have had a clinical fracture, the relative risk of recurrent fracture is highest between 1 and 2 years post-fracture. This risk remains more than 2-fold elevated at 10 years after the initial fracture and does not return to baseline levels for at least another decade. These fractures can be life-altering with many patients experiencing limitations in functioning.

The immediate 1 to 2 years post-fracture, when the relative and absolute risk of subsequent fracture is greatest, is when patients are in most need of effective pharmacologic intervention to increase bone mass and bone strength.

Clinical Development Program (Efficacy): The romosozumab clinical development program included a total of 19 studies, 7 of which were phase 2 and 3 studies. The two pivotal phase 3 PMO fracture studies and the phase 3 PMO study of romosozumab vs teriparatide are described below.

Pivotal phase 3 fracture Study 337 was a randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis. Subjects were randomized to 12 months of romosozumab followed by 12 months of denosumab or to 12 months of placebo followed by 12 months of denosumab. Romosozumab significantly reduced the risk of new vertebral fracture by 73% through month 12 and by 75% through month 24 (coprimary efficacy endpoints) as shown in Figure 1.

Figure 1. Coprimary Endpoints: New Vertebral Fracture (Study 337)



Absolute risk reduction (ARR) and relative risk reduction (RRR) are based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture stratification variables. P-values are based on separate logistic regression models adjusting for age and prevalent vertebral fracture stratification variables.

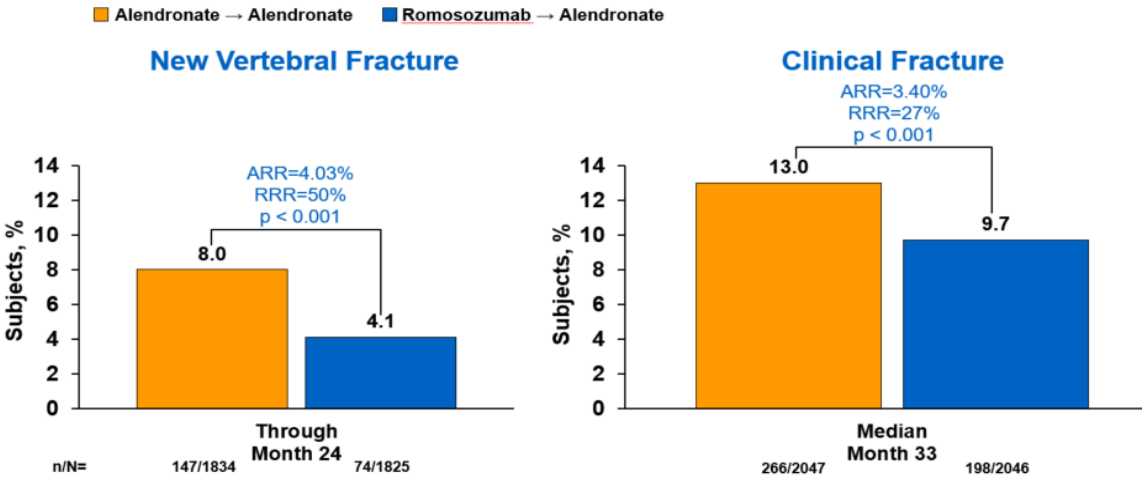
Pivotal phase 3 fracture Study 142 was a randomized, double-blind, alendronate-controlled study of romosozumab in postmenopausal women with osteoporosis at high risk for fracture and who had a prior fracture. Subjects were randomized to 12 months of romosozumab followed by alendronate or to alendronate alone.

Romosozumab followed by alendronate was superior to alendronate alone for reduction in new vertebral fracture through month 24 and clinical fracture at primary analysis, which was event-driven and occurred after a median 33 months on study; these were the 2 primary endpoints in the study. Primary analysis was performed when all subjects had completed the 24-month visit and clinical fractures were confirmed in > 330 subjects. Both primary endpoints were statistically significant for romosozumab/alendronate vs alendronate alone (Figure 2).

Secondary fracture endpoint results at the primary analysis (as defined above) included:

- **Nonvertebral fractures:** Romosozumab followed by alendronate resulted in a 19% lower relative risk of nonvertebral fracture compared with alendronate alone (p = 0.037) (absolute risk reduction [ARR] [95% CI], 1.90% [0.1, 3.7]); nonvertebral fractures occurred in 178 subjects (8.7%) in the romosozumab→alendronate group vs 217 subjects (10.6%) in the alendronate→alendronate group.
- **Hip fractures:** Romosozumab followed by alendronate resulted in a 38% lower relative risk of hip fracture compared with alendronate alone (nominal p = 0.015) (ARR, 1.20% [0.2, 2.2]); hip fractures occurred in 41 subjects (2.0%) in the romosozumab→alendronate group vs 66 subjects (3.2%) in the alendronate→alendronate group.

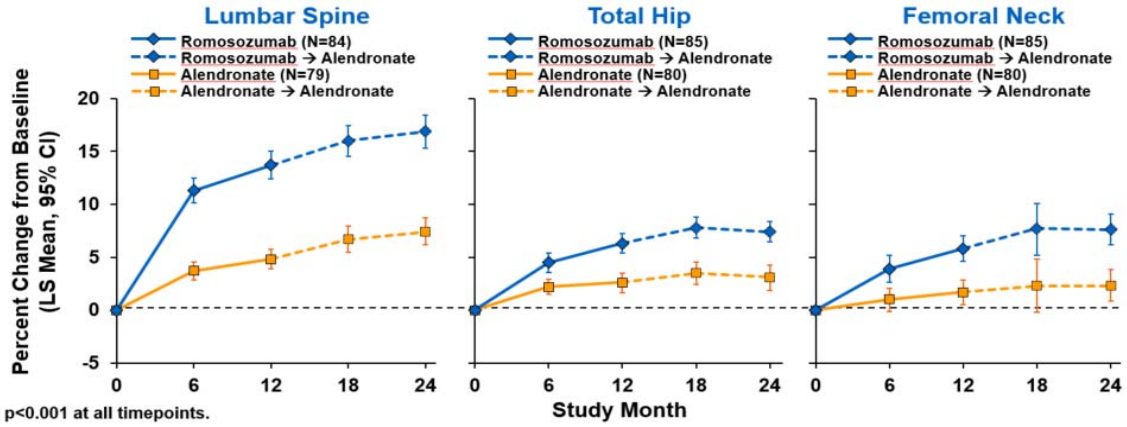
Figure 2. Primary Endpoints (Study 142)



Absolute risk reduction (ARR) for both new vertebral and clinical fractures and relative risk reduction (RRR) for new vertebral fractures are based on Mantel-Haenszel method. For clinical fractures, RRR is based on Cox proportional hazards model. Both methods adjust for baseline age strata, total hip BMD T-score, and presence of severe vertebral fracture.

Through month 12, romosozumab significantly increased the percent change from baseline in bone mineral density (BMD) compared with alendronate at the lumbar spine, total hip and femoral neck, with mean differences of 8.7%, 3.3%, and 3.2%, respectively (adjusted $p < 0.001$ for all 3 sites; Figure 3). Through month 24 (after 12 months of romosozumab or alendronate followed by alendronate for 12 months), significant increases continued (adjusted $p < 0.001$ for all 3 sites). The BMD increases were seen as early as month 6 (Figure 3).

Figure 3. BMD Over Time (Study 142)



ANCOVA = analysis of covariance; BMD = bone mineral density; N = Number of subjects enrolled in the Imaging and PK/Bone Turnover Marker/Biomarker substudy with values at baseline and at least 1 postbaseline visit at month 6 or month 18; PK = pharmacokinetics.
Point estimates, 95% confidence intervals, and p-values are based on ANCOVA model adjusting for treatment, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. P-value is for difference in treatment effect.
Missing values are imputed by carrying forward the last non-missing postbaseline value prior to the missing value and within the study period.

Phase 3 supportive Study 289 was a randomized, open-label teriparatide-controlled 12-month study in 436 women with PMO at high risk for fracture. Subjects transitioning from a bisphosphonate were randomized to 12 months of romosozumab or teriparatide. The study mirrors a common clinical scenario where patients who have been treated with a bisphosphonate become high risk for fracture and have to transition to a bone-forming agent. In this situation, teriparatide is less effective unless the bisphosphonate is washed out for several months.

The mean percent change from baseline through month 12 in BMD at the total hip was 2.6% (2.2%, 3.0%) in the romosozumab group and -0.6% (95% CI: -1.0%, -0.2%) in the teriparatide group. The mean differences in hip and spine BMD were statistically significant at month 6 and month 12 (Figure 10), as were other indices of bone strength at the hip compared with teriparatide.

Clinical Development Program (Safety): The safety profile of romosozumab was evaluated in 7518 subjects who have received at least one dose of romosozumab in a database including over 14 000 subjects. Romosozumab's key non-cardiovascular safety risks are hypersensitivity reactions, hypocalcemia, and rare cases of osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF). These risks are consistent with those of other osteoporosis products.

The main safety observation discussed in this document is the cardiovascular (CV) safety profile of romosozumab. Cardiovascular serious adverse events (CV SAEs) in Studies 337, 142, and 174 were centrally adjudicated by Duke Clinical Research Institute (DCRI), an independent academic adjudication committee.

In the 7180-subject pivotal placebo-controlled Study 337, there were 92 subjects with positively-adjudicated CV SAEs in the 12-month double-blind period with an identical incidence between the romosozumab and placebo groups: 46 (1.3%) in each group (Table 14). Incidences for positively-adjudicated myocardial infarction (MI), stroke, and CV death were generally balanced between groups; for romosozumab vs placebo, respectively, 9 (0.3%) vs 8 (0.2%) for MI; 8 (0.2%) vs 10 (0.3%) for stroke; and 17 (0.5%) vs 15 (0.4%) for CV death. The hazard ratio (HR) for time to first major adverse cardiac event (MACE), defined as CV death, MI, or stroke, at 12 months was 1.03 (0.62, 1.72) (Figure 4). During the overall study period of 36 months which includes the follow-on period after month 12 when all subjects received denosumab, the subject incidence of MI was 23 subjects (0.6%) in the romosozumab arm compared with 19 subjects (0.5%) in the placebo arm (Table 15). The incidence of stroke was 37 subjects (1.0%) in the romosozumab arm compared with 31 subjects (0.9%) in the placebo arm. The HR for time to first MACE at the end of the overall study period was 1.12 (0.83, 1.49) (Figure 4).

In the 4093-subject alendronate-controlled Study 142, there were 88 subjects with positively-adjudicated CV SAEs in the 12-month double-blind period. There was a higher incidence with romosozumab (50 [2.5%]) compared with alendronate (38 [1.9%]). The higher incidence was primarily driven by MI and stroke; incidences for romosozumab vs alendronate, respectively, were 16 (0.8%) vs 5 (0.2%) for MI and 13 (0.6%) vs 7 (0.3%) for stroke. The incidence of CV death was generally balanced between treatment groups: 17 (0.8%) vs 12 (0.6%) (Table 14). The HR for time to first MACE at 12 months was 1.87 (95% CI: 1.11, 3.14) (Figure 4). During the overall study period (median of 36 months), which includes the follow-on period after month 12 when all subjects received alendronate, the subject incidence of MI was balanced: 23 subjects (1.1%) in the romosozumab arm compared with 21 subjects (1.0%) in the alendronate arm (Table 15). The incidence of stroke was 42 (2.1%) in the romosozumab arm and

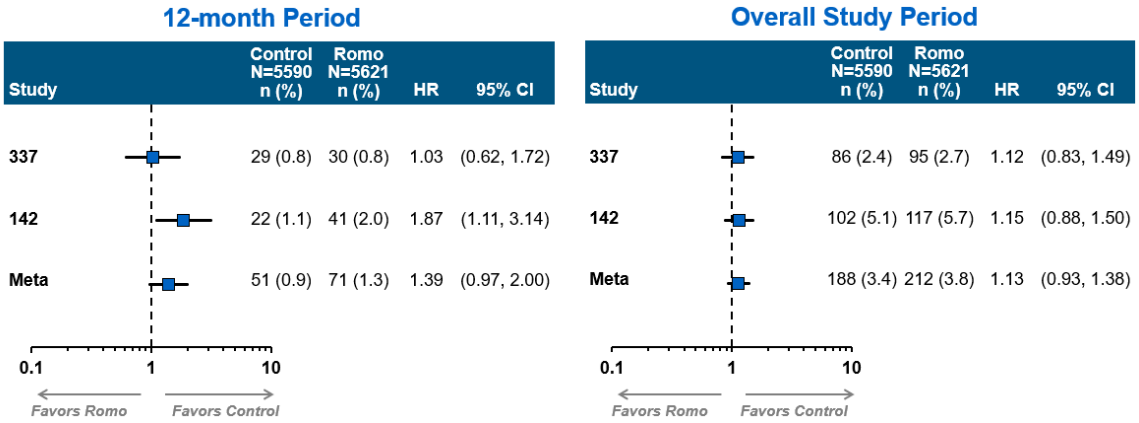
24 (1.2%) in the alendronate arm. The HR for time to first MACE at the end of the overall study period was 1.15 (95% CI: 0.88, 1.50) (Figure 4).

For the meta-analysis of Studies 337 and 142, the HR for time to first MACE was 1.39 (95% CI: 0.97, 2.00) for the 12-month double-blind treatment period and 1.13 (95% CI: 0.93, 1.38) for the overall study period (Figure 4).

Subgroup analyses of the meta-analysis did not identify any subpopulations in which the relative risk of MACE was higher with administration of romosozumab. This included subjects with a prior history of MI or stroke. These subjects did have a higher absolute risk with romosozumab compared with control.

Extensive nonclinical and clinical studies, including assessment of blood pressure, heart rate and electrocardiograms, did not identify any effects of romosozumab on the cardiovascular system that could explain the MACE outcome.

Figure 4. Time to First MACE Through Month 12 and the Overall Study Period (DCRI Adjudication of Studies 337 and 142, Individually and Meta-analysis)



HR = hazard ratio; Meta = meta-analysis; Romo = romosozumab

To summarize clinical safety, the non-CV safety of romosozumab was consistent with that of other osteoporosis therapies. Based upon the totality of the data, there is a possible risk of MI and stroke with romosozumab with a hazard ratio for MACE in the meta-analysis of 1.39 with the upper bound 95% CI of 2.00 in the 12-month double-blind treatment period and 1.13 with the upper bound 95% CI of 1.38 in the overall study period.

Benefit/Risk

There is a clear unmet need in women with osteoporosis at high risk for fracture, particularly those with a recent fracture, to strengthen bone and rapidly reduce fracture risk across the skeleton. It is anticipated that healthcare professionals will use romosozumab in this vulnerable patient population.

Through its dual mechanism of action, romosozumab rapidly increases BMD at the lumbar spine and hip, starting as early as 6 months; these gains were superior to both alendronate and teriparatide through 12 months of therapy and continued to accrue when transitioned to antiresorptive therapy. Romosozumab rapidly reduced fractures within 12 months. Long-term anti-fracture efficacy also continued after transition to antiresorptive therapy. This is the first large osteoporosis program to show anti-fracture efficacy across a range of anatomical sites (vertebral, clinical, and nonvertebral, including hip, fractures) compared with alendronate, the most commonly used

antiresorptive therapy. The reductions in fracture risk are clinically meaningful and important for women at high risk for fracture. In summary, romosozumab can benefit these patients who need a more potent bone-forming agent to rapidly reduce fracture risk.

Romosozumab's safety profile was evaluated in more than 14 000 subjects. Romosozumab's key safety risks from a non-cardiovascular standpoint are hypersensitivity reactions, hypocalcemia, and rare cases of ONJ and AFF. These risks are consistent with those of other osteoporosis products and all are manageable. There was a higher incidence of positively-adjudicated CV SAEs in the alendronate-controlled Study 142, which was driven by a higher incidence of MI and stroke. The incidence of positively adjudicated CV SAEs was identical between the romosozumab and placebo arms in the placebo-controlled Study 337. Given the modest number of CV SAEs in individual trials in the 12-month double-blind period, a meta-analysis was performed which showed a HR for time to first MACE of 1.39 (95% CI: 0.97, 2.00) at 12 months based on 122 MACE events and 1.13 (95% CI: 0.93, 1.38) for the entire study based on 400 MACE events.

Given the totality of the data, the benefit of marked fracture risk reduction in postmenopausal women at high fracture risk is weighed against the possible increased risk of MI and stroke that is estimated at a MACE HR of 1.39 with an upper-bound 95% CI of 2.00 at month 12 and 1.13 with an upper-bound 95% CI of 1.38 for the entire study. Labeling, including a boxed warning, is proposed to communicate this possible risk. In addition, a robust non-interventional post-marketing cohort study is planned to exclude a 2-fold risk of MACE in postmenopausal women at high fracture risk receiving romosozumab compared with those receiving other osteoporosis therapies. It is anticipated that data from this study will be available within 3 years post-approval. Evaluation of this possible risk in the intended US patient population and the timely data availability afford advantages over other trial options to further investigate the relationship between romosozumab and CV events. In conclusion, the benefit-risk of romosozumab in postmenopausal women at high risk for fracture is favorable, provided that the important possible risk of MI and stroke is effectively communicated in the USPI and further investigated post-marketing.

2. Product Information

2.1 Proposed Indication and Dosing

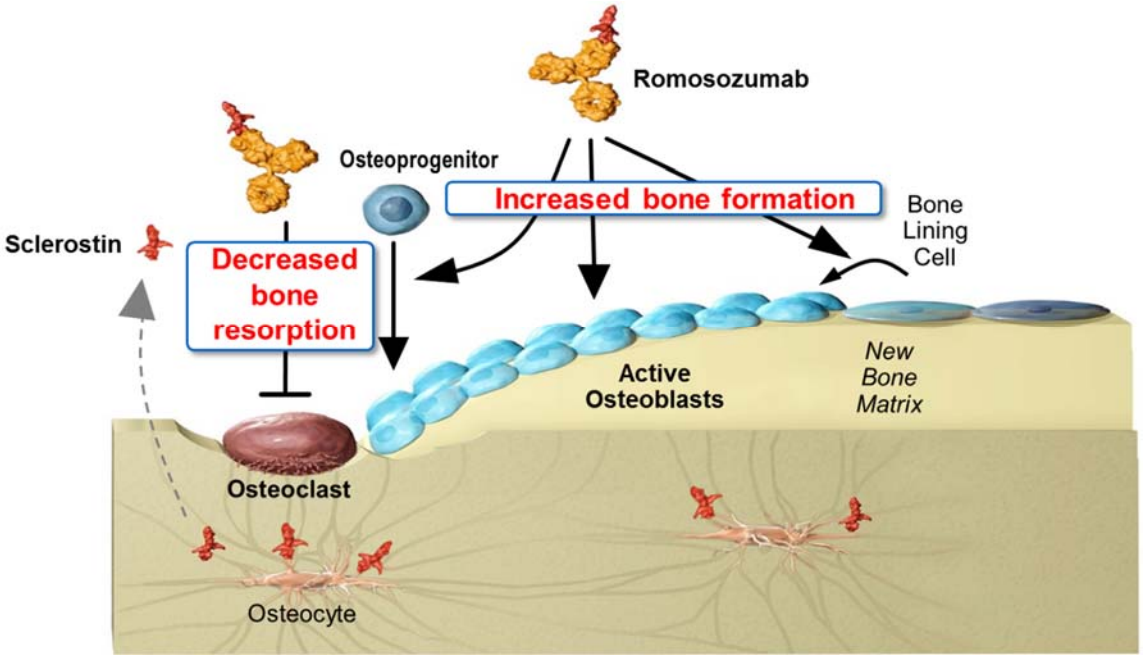
The proposed indication for romosozumab is treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

The proposed dosing recommendation is for sequential therapy with romosozumab 210 mg administered by subcutaneous (SC) injection monthly for one year followed by antiresorptive therapy.

2.2 Mechanism of Action

Romosozumab is a high-affinity humanized IgG_2 monoclonal antibody that binds sclerostin, an extracellular inhibitor of canonical Wnt signaling. Romosozumab neutralizes sclerostin's inhibitory function resulting in activation of canonical Wnt signaling, which promotes the dual action of bone formation and decreases bone resorption (Figure 5). Together this dual effect of increasing bone formation and decreasing bone resorption results in improvements in bone mass, structure, and strength.

Figure 5. Romosozumab Mechanism of Action



Boyce et al, 2018; Kim et al, 2017; Taylor et al, 2016; Ominsky et al, 2015. For sclerostin: *Atkins et al, 2011; Wijenayaka et al, 2011*

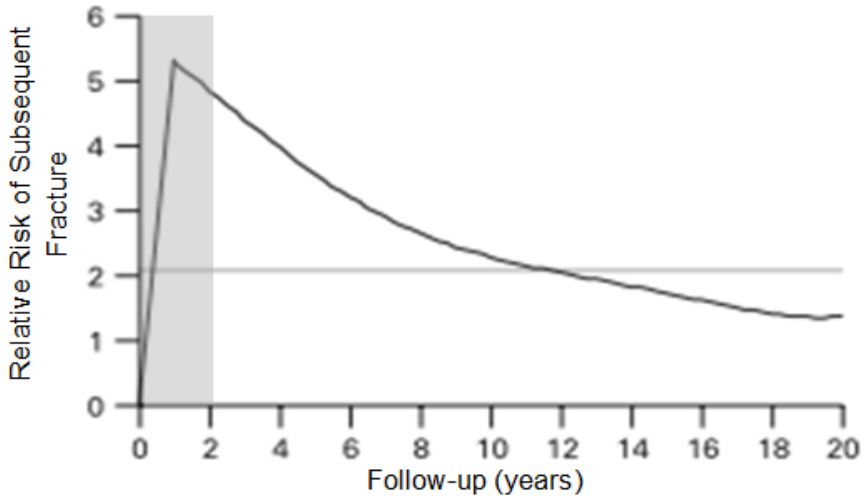
3. Burden of Disease and Limitations of Current Therapies for Women With Postmenopausal Osteoporosis at High Risk for Fracture

3.1 Burden of Disease

Osteoporosis is a well-recognized public health issue with increasing urgency due to the aging of the population (Khosla and Shane, 2016). Fracture is the single most important sequela of osteoporosis. In the US, osteoporosis-related fractures occur in approximately 1 in 2 Caucasian women who reach 50 years of age (NOF, 2018).

Patients suffering from an osteoporosis-related fracture have an increased risk for future fracture and with it, frailty. Among the most important determinants of risk for repeat fracture is the recency of the first fracture. It has been shown that the risk of the second fracture is greatest (> 5-fold) within the 1 to 2 years following the first fracture and remains greater than the risk pre-fracture for more than 20 years (Figure 6; Johansson et al, 2017; van Geel et al, 2009).

Figure 6. Relative Risk of Subsequent Fractures in Women Age 50 to 80 With Clinical Fractures



Relative risk of all subsequent fractures calculated as a mean from the first fracture (grey line) and per separate year of follow-up (black line).
Source: adapted from van Geel et al, 2009

In a study of over 377,000 postmenopausal women enrolled in US Medicare who sustained one or more clinical fractures, an initial fracture at any one of several major skeletal sites was associated with an absolute risk of second fracture at any skeletal site that increased over time: 8% to 12% within 1 year and 15% to 20% within 2 years following the initial fracture (Balasubramanian et al, 2018). Thus, the immediate 1 to 2 years post-fracture is when postmenopausal women most need a rapid, effective

pharmacologic intervention to increase bone mass and bone strength to reduce their risk of subsequent fracture and its sequelae.

Osteoporosis-related fractures are associated with physical disability and loss of independence. Vertebral fractures may result in pain, disability, fatigue, and deformity (Klazen et al, 2010; Suzuki et al, 2010; Fechtenbaum et al, 2005; Hasserius et al, 2005; O'Neill et al, 2004). Having a fracture alters balance and increase the risk of falls (McDaniels-Davidson et al, 2018; Hsu WL et al, 2014). Within 1 year after hip fracture, 40% of patients are unable to walk independently and 60% or more require assistance with activities of daily living (Cooper, 1997). Furthermore, a large study in the elderly US population reported that 20% of community-dwelling patients with hip fracture entered long-term nursing care within 1 year following their fracture, representing a 4-fold increased risk compared to matched patients without hip fracture (Tajeu et al, 2014).

The psychosocial aspects associated with fracture are important, yet often overlooked. In one study of women aged ≥ 75 years at high risk of hip fracture and who live in their homes, the majority (80%) of participants viewed death as preferable to hip fracture. They associated hip fracture with lowered quality of life, loss of independence, and subsequent admission to a nursing home (Salkeld et al, 2000).

Several observational studies have suggested that the absolute risk of death is higher for hip fracture, followed by vertebral and non-hip nonvertebral fracture (Morin et al, 2011; Schnell et al, 2010; Tran et al, 2017). In contrast, increased mortality has not been seen in placebo-controlled trials or in other large cohort studies with better ascertainment for the mortality endpoint.

3.2 Current Therapies and Unmet Need

Osteoporosis is a chronic disease and requires lifelong therapy. Antiresorptives and bone-forming agents comprise the current treatments for osteoporosis and are outlined in Table 1. In 2011 in the US, bisphosphonates were used by 83% of women who were using any pharmacologic osteoporosis therapy (Sarpong, 2014). Bisphosphonates are effective at reducing fracture occurrence over 3 to 5 years (Black et al, 2015; Black et al, 2012; Black et al, 2006; Mellstrom et al, 2004).

Table 1. Pharmacologic Therapies for Postmenopausal Osteoporosis

Category	Drug	Route and Frequency of Administration
Antiresorptives		
RANKL inhibitor	denosumab (Prolia®)	SC, every 6 months
Bisphosphonates	alendronate (Fosamax®)	oral, daily or weekly
	ibandronate (Boniva®)	oral, daily or monthly; IV, Q3M
	risedronate (Actonel®)	oral, daily, weekly, or monthly
	zoledronic acid (Reclast®)	IV, once yearly
Bone-forming Agents		
Bone-forming Agents (PTH and PTH-related protein analogs)	teriparatide (Forteo®)	SC, daily
	abaloparatide (Tymlos™)	SC, daily

IV = intravenous; PTH = parathyroid hormone; Q3M = every 3 months; RANKL = Receptor activator of nuclear factor kappa-B ligand; SC = subcutaneous. *Source: adapted from Baun and Russell, 2011*

For patients at high risk of fracture, denosumab, a RANKL inhibitor and potent antiresorptive, is a treatment option along with the 2 currently approved bone-forming therapies, the parathyroid hormone (PTH) analog, teriparatide, and the PTH-related protein analogue, abaloparatide. Bone-forming agents are recommended to be used for no more than a life-time maximum of 2 years due to the risk of osteosarcoma identified in rat models. Bone-forming agents are typically used for shorter periods of time than antiresorptive agents, and reduce fracture risk in patients who are at high risk for fracture at earlier timepoints than in historial trials of antiresorptives.

Sequential treatment with a bone-forming agent followed by an antiresorptive is well-established (Cosman et al, 2017; Black et al, 2006; Prince et al, 2005; Lindsay et al, 2004). The gains in bone mass and the improvement in bone strength that will translate to fracture risk reduction have been shown to be maintained with sequential treatment with an antiresorptive agent (Cosman et al, 2017; Prince et al, 2005).

For patients who are vulnerable to fracture, especially those who need rapid fracture risk reduction and those currently taking antireorptive therapy, there are no treatment options that can rapidly establish a robust foundation of increased mass at all skeletal sites that will be maintained even after patients are transitioned to antiresorptive therapy.

4. Preclinical Safety and Toxicology

A comprehensive series of toxicology studies were performed in rats and cynomolgus monkeys to characterize the nonclinical toxicology profile of romosozumab. Nonclinical toxicology data indicated no safety concern for human use. In chronic bone quality studies in ovariectomized (OVX) rats and cynomolgus monkeys, romosozumab dose-dependently increased bone formation and bone mass and improved bone architecture while maintaining bone quality; no safety issues were observed.

4.1 Carcinogenicity

Romosozumab does not pose a carcinogenic risk based on scientific weight-of-evidence and findings from a lifetime pharmacology study in rats.

4.2 Nonclinical Cardiovascular Considerations

Sclerostin is constitutively expressed in the aorta of mice, monkeys, and humans; however, the function of sclerostin in the vasculature is unclear. Sclerostin was reported to be upregulated in areas of vascular calcification in mice, rats and humans (Brandenburg et al, 2016; Rukov et al, 2016; Kramann et al, 2013; Koos et al, 2013; Zhu et al, 2011). It was demonstrated to inhibit mineralization in bone cell cultures by inhibiting differentiation of osteoblasts to a mineralizing phenotype (Atkins et al, 2011; Li et al, 2009); therefore, sclerostin was hypothesized to inhibit vascular calcification. In addition, sclerostin was hypothesized to inhibit atheroprogression and systemic inflammation (Krishna et al, 2017). To evaluate the role of sclerostin in the vasculature and the potential effects of sclerostin inhibition on the CV system, Amgen conducted several in vivo and in vitro nonclinical studies and reviewed the literature. A clear function of sclerostin in the vasculature was not identified. The totality of nonclinical data indicate that sclerostin inhibition does not adversely affect CV function and does not promote vascular calcification or atheroprogression.

Sclerositn inhibition did not affect CV functional endpoints in monkeys and in isolated human coronary artery rings. Studies demonstrated:

- no acute or chronic effects on CV functional parameters (electrocardiogram, arterial blood pressure, heart rate, and respiratory rate) in instrumented monkeys
  - following a single intravenous dose (300 mg/kg) of romosozumab providing area under the curve (AUC) and maximum serum concentration (C_{max}) margin to clinical exposure at 210 mg of approximately 32- and 210-fold, respectively, or
  - following 6 months of repeat dosing (electrocardiograms and blood pressure) at exposures up to 93-fold greater than clinical exposure based on AUC.
- no effects of romosozumab or recombinant sclerostin were observed on vasoconstriction, in contrast to sumatriptan, in a human coronary artery ring assay at concentrations up to approximately 10-fold greater than clinical C_{max} or reported average serum sclerostin concentration in postmenopausal women (Mödder et al, 2011), respectively

Inhibition or absence of sclerostin did not result in the initiation or exacerbation of vascular calcification in monkeys, rats and mice. Studies showed:

- no macroscopic or microscopic evidence of vascular abnormalities or mineralization in 6-month, repeat-dose toxicity study in monkeys, dosed with romosozumab at up to 93 times the clinical exposure
- no radiographic evidence of aortic vascular mineralization in aged OVX monkeys (a model for PMO) dosed with romosozumab for 1 year at 22 times the clinical exposure[2]
- no exacerbation of spontaneous age-related vascular calcification characterized by focal medial calcification or ectopic ossification in rats following lifetime exposure to romosozumab at up to 19 times the clinical exposure
- in the context of the pro-calcific milieu of experimental chronic renal disease, no exacerbation of aortic medial calcification in rats treated with sclerostin antibody (Moe et al, 2015) or promotion of medial calcification in the total absence of sclerostin in Sost knockout (KO) mice (Kaesler et al, 2018).

In light of the CV safety observations in the phase 3 Study 142, additional nonclinical studies evaluated the potential risk of sclerostin inhibition for acute CV events:

- No platelet activation was observed in vitro at romosozumab concentrations up to approximately 10-fold greater than clinical Cmax
- Sclerostin expression was assessed in human atherosclerotic plaques in endarterectomy samples of carotid and femoral arteries.
  - Immunohistochemical staining revealed sclerostin expression was absent in the majority of plaques. When present, reduced expression was observed in the media of plaques compared with normal aorta and was limited to the media and immediate subjacent subintima.
  - Sclerostin was not expressed in the endothelial or fibrous caps, locations relevant to plaque stability.

  - There was no correlation of sclerostin expression with age at endarterectomy, history of arterial disease, or cardiac outcomes.
  - There was no correlation of sclerostin expression with plaque pro-inflammatory cytokine profile, intraplaque hemorrhage, macrophage infiltration, collagen content, smooth muscle cell content, or lipid core size.

- In light of the study published by Krishna et al, 2017 proposing that sclerostin functions as an inhibitor of atheroprogression and systemic inflammation in angiotensin II-infused male apolipoprotein E (ApoE) KO, a study was conducted in high fat diet-fed ApoE KO OVX mice, a widely-used experimental model of atherogenesis, to evaluate the effects of sclerostin antibody on atheroprogression over 16 weeks of treatment.
  - Results showed that treatment with sclerostin antibody at exposures predicted to be 4-fold greater than clinical exposure did not increase total plaque volume or mineralized plaque volume.
  - In addition, sclerostin antibody had no effect on transcriptional pathways or histologic changes in aortic atherosclerotic plaques associated with the ApoE KO genotype or on the presence of circulating inflammatory cytokines.
  - Finally, sclerostin expression decreased with progression of atherosclerosis, and expression was unaffected by administration of sclerostin antibody.
- Public databases of genome-wide association studies were examined to identify any associations of single nucleotide polymorphisms (SNPs) near the SOST locus with stroke or myocardial infarction (MI). The major allele C of SNP rs2741856, which has the most significant BMD association at the SOST locus reported in the literature and is associated with reduced sclerostin expression in the aorta and tibial artery, was used for this investigation (Medina-Gomez et al, 2018; MacArthur et al, 2017). This study concluded that natural genetic modulation of SOST by SNP rs2741856 has a significant positive effect on bone physiology, but no detectable effect on risk of MI or stroke.

In summary, no biologically plausible mechanism for the increase in MI or stroke events observed in alendronate-controlled Study 142 was identified.

5. Clinical Development Program

Romosozumab was investigated in 19 clinical studies conducted between 2006 and 2017 that enrolled approximately 14 000 subjects. The clinical development program included:

- 12 phase 1 clinical pharmacology studies including 5 bioavailability/bioequivalence studies
- 2 phase 2 dose-ranging studies
- 4 phase 3 studies in women with PMO
- 1 phase 3 study in men with osteoporosis

Key study design features across all of the phase 2 and phase 3 studies are described in Appendix 1.

Of these studies, the phase 2 Study 326 was used to determine the current dosing strategy in women with PMO. Studies 337 and 142 were the pivotal phase 3 PMO fracture prevention trials. The phase 3 Study 289 evaluated postmenopausal women with osteoporosis transitioning from bisphosphonates to either romosozumab or teriparatide. While the phase 3 male osteoporosis Study 174 does not support this indication, the safety data is briefly discussed as part of the comprehensive CV safety evaluation. Endpoints in these studies assess the effect of romosozumab on the subject incidence of various fractures, percent change from baseline in BMD, and percent change from baseline in bone turnover markers. The efficacy and safety of romosozumab was compared against placebo and the most commonly used antiresorptive and bone-forming therapies, alendronate and teriparatide, respectively.

The primary evidence for the efficacy and safety of romosozumab for the treatment of osteoporosis in postmenopausal women was derived from 2 pivotal fracture studies, Studies 337 and 142, described in Section 6.4 and Section 6.5, respectively.

5.1 Regulatory History

Amgen submitted a Biologics License Application (BLA 761062) for romosozumab for the treatment of women with PMO at increased risk of fracture in July 2016. The submission was based on the positive results of the FDA agreed clinical development program including anti-fracture evidence from a single study, the placebo-controlled fracture Study 337. These studies demonstrated no imbalance in CV events. During the review period, Study 142, an alendronate-controlled pivotal phase 3 study in women at high risk for fracture was under way to support a regulatory submission in the European Union. Upon its completion, an unanticipated higher incidence of positively-adjudicated

cardiovascular serious adverse events (CV SAEs) was observed with romosozumab. In May 2017, a meeting was held between Amgen and the FDA to review the preliminary results of Study 142; a complete response letter was subsequently issued. This letter indicated that the FDA required a complete analysis of Study 142 and an integrated assessment of CV risk based on Studies 337, 142 and 174. The BLA was resubmitted in July 2018.

Based on romosozumab's efficacy and safety data, Amgen seeks an indication for the treatment of postmenopausal women with osteoporosis at high risk for fracture (see Section 2.1). To date the FDA have two indication statements for the treatment of osteoporosis: (1) a general osteoporosis population and (2) a high-risk osteoporosis population.

6. Efficacy

Efficacy of romosozumab in PMO is supported by Studies 326, 289, 337, and 142. Key study design features are described in Appendix 1. Fracture and BMD enrollment criteria, which determine osteoporosis severity and fracture risk, are described in Appendix 6 and below.

6.1 Phase 2 Dose Finding Study 326

Study Design: Study 326 was a randomized, placebo- and active-controlled, double-blind, phase 2a dose-ranging study in postmenopausal women with low BMD. Subjects were randomized to 1 of 5 double-blind dosing regimens of romosozumab (70, 140, 210 mg SC monthly or 140 or 210 mg SC every 3 months), placebo, open-label alendronate, or open-label teriparatide. The study evaluated romosozumab treatment for 24 months (Figure 7).

Diagnosis and Main Criteria for Eligibility: The population for the study was postmenopausal women (age ≥ 55 to ≤ 85) with low BMD at the lumbar spine, total hip, or femoral neck (BMD T-score ≤ -2.0 with lower limit of -3.5)

Efficacy Endpoints:

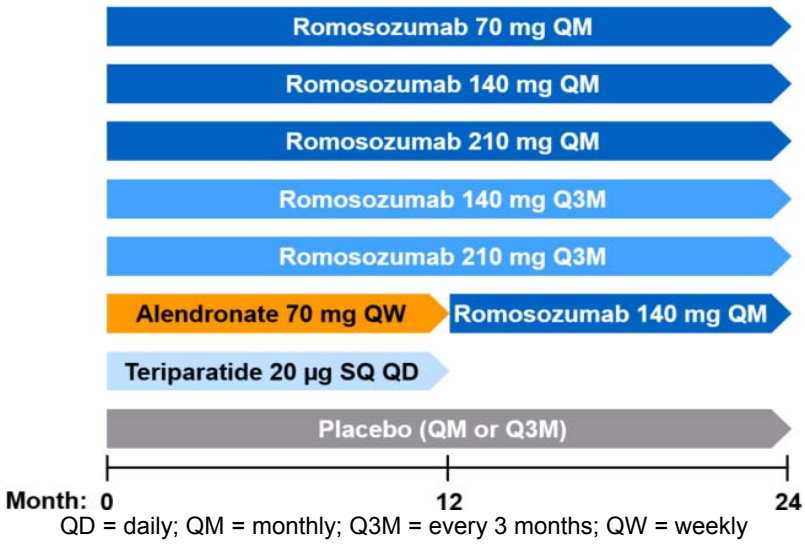
Primary Endpoint:

- percent change from baseline at month 12 in lumbar spine BMD

Secondary Endpoints:

- percent change from baseline at month 6 in lumbar spine, total hip, and femoral neck BMD
- percent change from baseline at month 12 in total hip, femoral neck, and distal radius BMD

Figure 7. Study Design for Dose-Ranging Portion of Study 326



QD = daily; QM = monthly; Q3M = every 3 months; QW = weekly

Subject Disposition: In total, 419 subjects were randomized: 51 to 54 subjects were randomized into each of the 5 romosozumab dose groups, 52 subjects to the placebo arm, 55 subjects to the teriparatide arm, and 51 subjects to the alendronate arm. A total of 383 subjects (91%) completed 12 months of study and 36 subjects (9%) withdrew before completing 12 months, 9 of whom never received investigational product. A total of 300 subjects (82%) completed 24 months of study and 15 subjects (4%) withdrew between 12 and 24 months, all of whom received investigational product.

Baseline Demographics: The baseline demographics among subjects enrolled into the study were comparable across the 8 arms. The mean age was 66.8 years (range: 55 to 84 years) and 86.4% of subjects were white.

Efficacy Results:

Baseline to Month 12 (Primary Analysis): At month 12, the mean percent changes from baseline in lumbar spine BMD in the romosozumab groups increased with dose from 5.4% for 70 mg monthly to 11.3% for 210 mg monthly, compared with -0.1% in the placebo group. Increases for all romosozumab groups were statistically significantly greater than placebo ($p < 0.001$). Statistically significant increases were seen for the romosozumab 140 mg and 210 mg monthly groups vs alendronate and teriparatide (Table 2).

Baseline to Month 24 (Exploratory Analysis): At month 12, subjects in the romosozumab and placebo groups continued their assigned treatment for an additional 12 months, subjects in the teriparatide group ended study participation, and subjects in the alendronate group transitioned to receive romosozumab 140 mg monthly for an

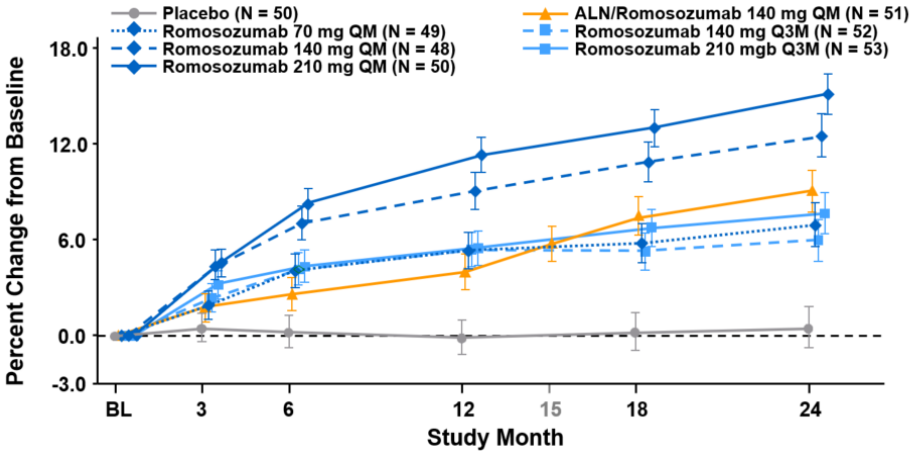
additional 12 months (months 12 to 24). From months 12 to 24, all monthly romosozumab dose regimens continued to show increases in BMD at the lumbar spine, total hip, and femoral neck with the greatest increases in the romosozumab 210 mg monthly group. Compared with the placebo group, each of the romosozumab groups showed significantly increased lumbar spine BMD ($p < 0.001$) at months 18 and 24 (Figure 8). Switching from alendronate to romosozumab at month 12 accelerated BMD gains, as shown by the orange line in Figure 8.

Table 2. Percent Change From Baseline in Lumbar Spine BMD Month 12 (Study 326 Primary Analysis)

	Placebo	ALN PO	TPTD SC	Romosozumab SC				
	Total (N = 50)	70 mg weekly (N = 51)	20 µg QD (N = 49)	70 mg QM (N = 49)	140 mg Q3M (N = 52)	140 mg QM (N = 48)	210 mg Q3M (N = 53)	210 mg QM (N = 50)
Month 12								
n	47	47	46	44	49	46	51	49
LS Mean	-0.1	4.1	7.1	5.4	5.4	9.1	5.5	11.3
95% CI	(-1.2, 0.9)	(3.0, 5.1)	(6.1, 8.2)	(4.3, 6.4)	(4.4, 6.5)	(8.0, 10.2)	(4.4, 6.6)	(10.3, 12.4)
Difference from Placebo [a]								
p-value				<0.001	<0.001	<0.001	<0.001	<0.001

ALN = alendronate; PO = orally; QD = every day; QM = once monthly; Q3M = every 3 months; TPTD = teriparatide
[a] p-value is adjusted by the Hochberg procedure for comparison to placebo.
Source: Table 10-2, 326 PA CSR

Figure 8. Percent Change From Baseline in BMD at the Lumbar Spine Over 24 Months (Study 326)



N = Number of subjects randomized and have baseline and at least one post baseline BMD measurements on or prior to the month 12; QM = monthly
Linear mixed effects model with the percent change from baseline to months 3, 6, 12, 15, 18 and 24 in BMD as dependent variable, and baseline BMD value, machine type, geographic region, interaction of baseline BMD and machine type, visit, treatment (categorical) and interaction of treatment and visit as the independent variables. Data after month 24 are excluded from the models Subjects randomized to ALN (alendronate) arm switched to romosozumab 140 mg QM at month 12.
Source: 326 CSR, Figure14q-4.2.1

6.2 Support for Romosozumab 210 mg SC QM Dosing for 12 Months

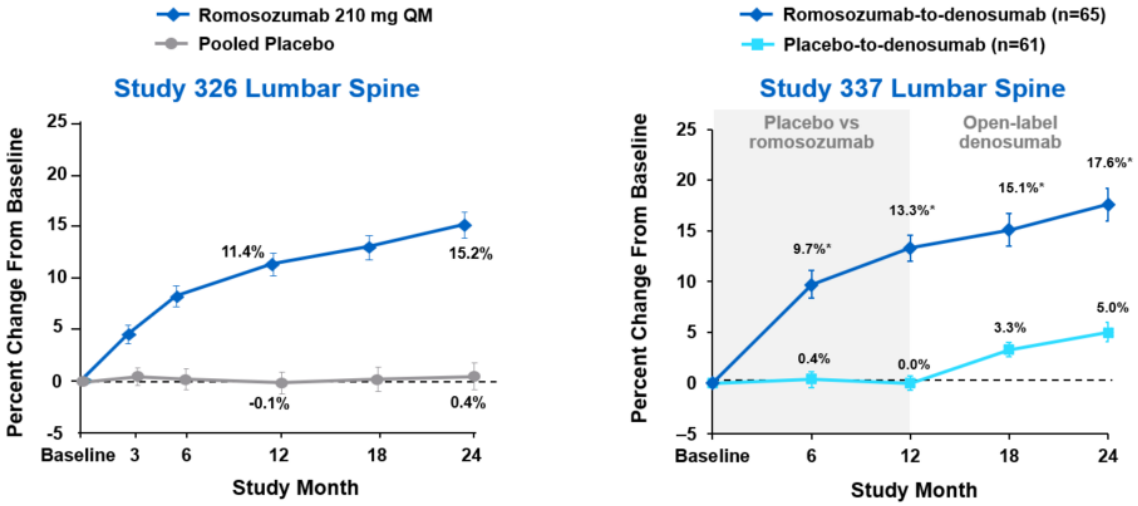
The romosozumab 210-mg monthly dosing regimen was selected based on the following phase 2 Study 326 data:

- The 210-mg monthly dosing regimen resulted in the greatest increase in BMD at the lumbar spine and total hip compared with other romosozumab dosing groups (Figure 8 lumbar spine results).
- The 210-mg monthly dosing regimen resulted in a greater increase in BMD at the lumbar spine, total hip, and femoral neck compared with the 2 active controls, alendronate and teriparatide (see Table 2 for lumbar spine results).
- The incidence of adverse events in the phase 2 study was not dose related, and the incidence of neutralizing antibodies against romosozumab was low and similar across doses (Section 7.5). Thus, the safety and tolerability of the 210-mg monthly dose was similar to the lower doses.

The duration of romosozumab treatment in the phase 3 program was limited to 12 months as the majority of benefit, as measured by BMD, occurred during the first 12 months of therapy. This is illustrated in Figure 8 and Figure 9 for Study 326 where subjects received romosozumab up to 24 months. The selection of a 12-month treatment period was validated by the BMD gains observed in Study 337 from month 12 to month 24 when subjects had transitioned to denosumab treatment (right side of Figure 9). The gains in BMD between months 12 and 24 in Study 337 (4.3%) that evaluated sequential treatment of romosozumab followed by denosumab were similar to

the gains in Study 326 over the same time frame on romosozumab alone (3.8%). As safety and tolerability were similar across all dosing regimens evaluated, safety observations did not influence the decision to limit romosozumab treatment to 12 months.

Figure 9. Comparison of Lumber Spine BMD Increases Over 24 Months in Study 326 and in Study 337



Source: CSRs 326 and 337

6.3 Phase 3 Supportive Study 289

Study Design: Study 289 (N = 436) was a phase 3 teriparatide-controlled study in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy to romosozumab or teriparatide. This study was designed to evaluate the percent change from baseline in BMD through 12 months of treatment with romosozumab 210 mg monthly compared with teriparatide 20 µg SC daily, following treatment with bisphosphonate, a common clinical scenario in patients at high risk for fracture. In this situation, teriparatide is much less effective unless the bisphosphonate is washed out for several months prior to the start of teriparatide.

Main Criteria for Eligibility:

Subjects were postmenopausal women, age 55 to 90 years, with a BMD T-score at the lumbar spine, total hip, or femoral neck of less than or equal to -2.5 and any history of nonvertebral fracture after age 50 or vertebral fracture at any time.

Subjects must have been taking an oral bisphosphonate at a dose approved for the treatment of PMO for a minimum of 3 years prior to randomization, with the last year (of the 3 years on an oral bisphosphonate) exclusive to alendronate (70 mg weekly or equivalent).

Efficacy Endpoints:

The primary endpoint was the percent change from baseline in BMD at the total hip through month 12.

Key secondary endpoints were the percent change from baseline in the following:

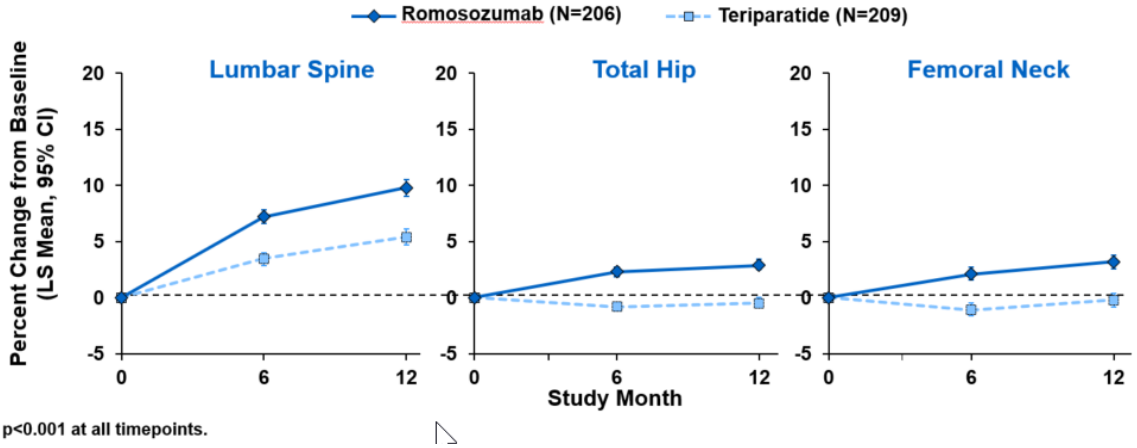
- BMD at the total hip at month 6 and at month 12
- Cortical BMD by quantitative computed tomography (QCT) at the total hip at month 6 and at month 12
- Integral BMD by QCT at the total hip at month 6 and at month 12
- Estimated strength by finite element analysis (FEA) at the total hip at month 6 and at month 12

Subject Disposition: A total of 436 subjects were randomized into the study (218 subjects per treatment group). Twenty (9.2%) subjects in the romosozumab group and 18 (8.3%) subjects in the teriparatide group discontinued the study.

Baseline Demographics: The baseline demographic and disease characteristics among subjects enrolled into the study were comparable between both treatment groups. The mean age was 71.5 years (range: 56 to 90 years), and 88.8% of subjects were white.

Efficacy Results: *Primary efficacy:* The mean percent change from baseline through month 12 in BMD at the total hip was 2.6% (95% CI: 2.2%, 3.0%) in the romosozumab 210 mg monthly group and -0.6% (95% CI: -1.0%, -0.2%) in the teriparatide 20 µg SC daily group. The mean difference between the 2 treatments was 3.2% (95% CI: 2.7%, 3.8%), which was statistically significant in favor of romosozumab ($p < 0.001$) (Figure 10).

Figure 10. Percent Change From Baseline in BMD at Lumbar Spine, Total Hip, and Femoral Neck Over 12 Months (Study 289)



N = number of subjects in primary efficacy analysis set for DXA endpoints; n = Number of subjects with values at baseline and at the time point of interest. Based on a repeated measures model adjusting for treatment, visit, baseline serum CTX value, baseline BMD value, machine type, baseline BMD value-by-machine type interaction, treatment-by-visit interaction, and using an unstructured variance covariance structure. P-value is for differences in treatment effect.
Source: Figure f-bm-repeat-dbmd-pchg-289

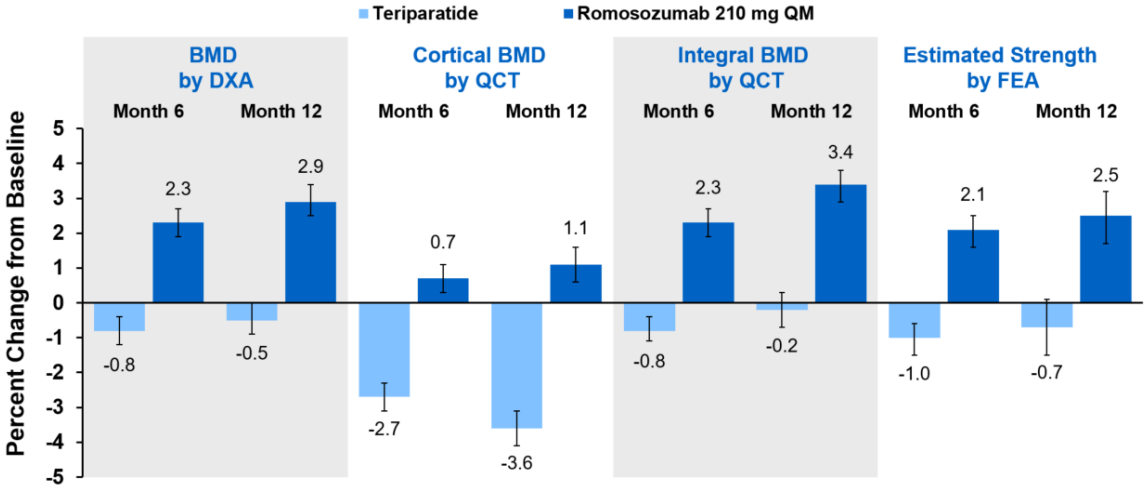
Key secondary endpoints:

Hip Strength: The mean differences in hip BMD were statistically significant at months 6 and 12, as were other indices of bone strength at the hip (Figure 11), showing an early benefit of romosozumab over the bone-forming drug, teriparatide.

Finite element analysis (FEA): FEA is a validated computational technique widely used in engineering to estimate the mechanical behavior of structures under loading.

Results for the secondary efficacy endpoints, estimated strength by FEA at the total hip at months 6 and 12, are provided in Figure 11. The mean difference between romosozumab and teriparatide at month 6 and at month 12 were significant ($p < 0.001$), demonstrating that romosozumab improved bone strength at the total hip in subjects transitioning from bisphosphates.

Figure 11. Increase in Indices of Bone Strength at the Hip With Romosozumab Compared With Teriparatide (Study 289)



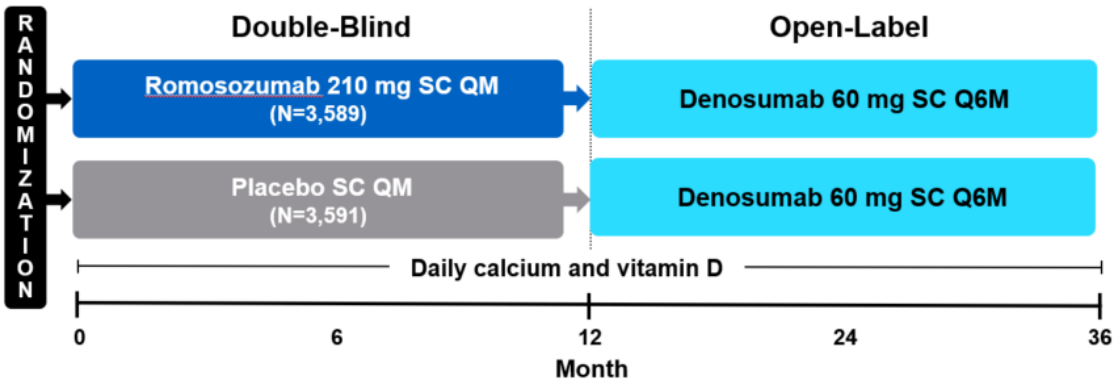
All p-values were < 0.001 with multiplicity adjustment. BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FEA = finite element analysis; QCT = quantitative computed tomography.
Source: CSR 289; *Langdahl B et al. Lancet. 2017; 390:1585–94.*

6.4 Phase 3 Pivotal Study 337

6.4.1 Study Design

As discussed above, both postmenopausal fracture outcome trials evaluated a sequential therapy of one year of romosozumab followed by antiresorptive therapy as it was anticipated that sustained benefit of romosozumab would be seen. For Study 337, the antiresorptive was denosumab, and for Study 142, it was alendronate. The study design for Study 337 is shown in Figure 12.

Figure 12. Study Design of Study 337



6.4.2 Enrollment Criteria

Placebo-controlled Study 337 enrolled a population of postmenopausal women at risk for osteoporosis-related fracture. Subjects in this study:

- had a baseline BMD T-score at the total hip or femoral neck of ≤ -2.5 at the total hip or femoral neck (lower limit of -3.5) and
- were excluded if they had experienced a hip fracture at any time or had any severe or more than 2 moderate vertebral fractures.

6.4.3 Efficacy Endpoints

The coprimary endpoints in Study 337 were:

- subject incidence of new vertebral fracture through 12 months (romosozumab vs placebo) and
- subject incidence of new vertebral fracture through 24 months (romosozumab followed by denosumab vs placebo followed by denosumab)

Key secondary endpoints were tested sequentially to control for multiplicity in the following order: clinical fracture (month 12), nonvertebral fracture (month 12 and month 24), clinical fracture (month 24), and 3 others fracture endpoints (see Figure 32).

6.4.4 Statistical Methodology

The statistical methods used in the pivotal fracture studies to analyze fractures, BMD, and bone turnover marker endpoints are summarized in Appendix 3.

The endpoints that were part of the fixed-sequence testing procedure are shown in Figure 32 for Study 337 and Figure 33 for Study 142. The term “nominal” is used for p-values < 0.05 calculated from statistical tests without adjusting for multiplicity.

6.4.5 Demographics and Baseline Characteristics

The placebo-controlled fracture Study 337 enrolled subjects with osteoporosis requiring treatment. Subjects were at risk for fracture with 18.3% of subjects with at least 1 verified prevalent vertebral fracture at baseline, most of which were mild or moderate in severity, and 22% of subjects with a history of nonvertebral fracture at or after age 45.

More than half of randomized subjects were white. Due to prespecified exclusion criteria and washout periods, a minority of subjects (< 10%) had used osteoporosis treatment medications before enrollment. Baseline characteristics were similar between treatment groups.

Table 3. Baseline Characteristics in Pivotal Fracture Studies (337 and 142)

	Study 337		Study 142	
	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM (N = 2046)
Ethnicity - n (%)				
Hispanic or Latino	1416 (39.4)	1427 (39.8)	662 (32.3)	631 (30.8)
Not Hispanic or Latino	2175 (60.6)	2162 (60.2)	1385 (67.7)	1415 (69.2)
Race – n (%)				
White	2052 (57.1)	2063 (57.5)	1415 (69.1)	1447 (70.7)
Asian	441 (12.3)	425 (11.8)	149 (7.3)	137 (6.7)
Black or African American	74 (2.1)	77 (2.1)	23 (1.1)	19 (0.9)
American Indian/Alaska Native	63 (1.8)	64 (1.8)	7 (0.3)	5 (0.2)
Native Hawaiian/Other Pacific Islander	1 (< 0.1)	0 (0.0)	2 (< 0.1)	0 (0.0)
Multiple	59 (1.6)	60 (1.7)	4 (0.2)	2 (< 0.1)
Other	901 (25.1)	900 (25.1)	446 (21.8)	436 (21.3)
Age				
Mean (SD) (years)	70.8 (6.9)	70.9 (7.0)	74.2 (7.5)	74.4 (7.5)
Age ≥ 75 years – n (%)	1121 (31.2)	1119 (31.2)	1071 (52.3)	1073 (52.4)
BMI (kg/m^2)				
Mean (SD)	24.74 (4.42)	24.66 (4.30)	25.36 (4.42)	25.46 (4.41)
Years since menopause - mean (SD)	23.07 (9.11)	22.98 (8.80)	26.85 (9.19)	26.94 (9.37)
Lumbar spine BMD T-score - mean (SD)	-2.71 (1.04)	-2.72 (1.04)	-2.99 (1.24)	-2.94 (1.25)
Total hip BMD T-score - mean (SD)	-2.46 (0.47)	-2.48 (0.47)	-2.81 (0.67)	-2.78 (0.68)
Prior fracture at or after age 45 - n (%)				
Osteoporotic	1258 (35.0)	1270 (35.4)	2029 (99.1)	2022 (98.8)
Nonvertebral	782 (21.8)	778 (21.7)	770 (37.6)	767 (37.5)
Prevalent vertebral fracture - n (%)				
At least one	645 (18.0)	672 (18.7)	1964 (95.9)	1969 (96.2)
Severe	4 (0.1)	1 (< 0.1)	1321 (64.5)	1369 (66.9)
Previous hip fracture [b]	NA[a]	NA[a]	179 (8.7) [b]	175 (8.6) [b]

NA = not applicable; Q1 = first interquartile; Q3 = third interquartile
[a] Exclusion criteria in Study 337
[b] From Saag et al, 2017
Prior osteoporotic fractures include both prevalent vertebral fractures and nonvertebral fractures, excluding high trauma and pathologic fractures.
Source: SCE Resubmission, Table 14-2.6 CSR142, Table 14-2.6 CSR337; ISE Table 14e-2.1

6.4.6 Subject Disposition

About 89% of subjects completed the 12-month double-blind treatment period (Table 4). The most frequent reason for discontinuation was withdrawn consent. The number and percent of subjects who discontinued the study at later time periods are provided in the table below.

Table 4. Subject Disposition and Investigational Product Completion (Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3591) n (%)	Romosozumab 210 mg QM (N = 3589) n (%)	Alendronate 70 mg QW (N = 2047) n (%)	Romosozumab 210 mg QM (N = 2046) n (%)
Completed double-blind study period	3205 (89.3)	3185 (88.7)	1823 (89.1)	1831 (89.5)
Discontinued double-blind study period[a]	386 (10.7)	404 (11.3)	224 (10.9)	215 (10.5)
Consent withdrawn	253 (7.0)	261 (7.3)	139 (6.8)	129 (6.3)
Adverse event	39 (1.1)	39 (1.1)	25 (1.2)	25 (1.2)
Other	24 (0.7)	34 (0.9)	6 (0.3)	9 (0.4)
Death	20 (0.6)	27 (0.8)	24 (1.2)	27 (1.3)
Lost to follow-up	21 (0.6)	22 (0.6)	16 (0.8)	13 (0.6)
Noncompliance	16 (0.4)	9 (0.3)	4 (0.2)	7 (0.3)
Ineligibility	6 (0.2)	7 (0.2)	5 (0.2)	2 (<0.1)
Investigational product (IP) accounting				
Never received IP	9 (0.3)	14 (0.4)	7 (0.3)	8 (0.4)
Completed double-blind IP	3135 (87.3)	3103 (86.5)	1738 (84.9)	1750 (85.5)
Discontinued double-blind SC IP[a]	447 (12.4)	472 (13.2)	288 (14.1)	278 (13.6)
Consent withdrawn	252 (7.0)	259 (7.2)	148 (7.2)	127 (6.2)
Adverse event	92 (2.6)	100 (2.8)	65 (3.2)	68 (3.3)
Death	18 (0.5)	20 (0.6)	20 (1.0)	22 (1.1)
Other	35 (1.0)	36 (1.0)	26 (1.3)	22 (1.1)
Lost to follow-up	24 (0.7)	28 (0.8)	14 (0.7)	17 (0.8)
Noncompliance	15 (0.4)	16 (0.4)	10 (0.5)	15 (0.7)
Discontinued 24-month study period (337 only)	559 (15.6)	595 (16.6)	-	-
Discontinued primary analysis study period (142 only)[b]	-	-	471 (23.0)	472 (23.1)
Discontinued overall study period (36 months for 337; end of study for 142[c])	699 (19.5)	738 (20.6)	544 (26.6)	523 (25.6)

[a] Reasons for discontinuation are listed if they occurred in 5 or more subjects in any treatment group in either study.
[b] Primary analysis study period was a median of 33 months (interquartile range of 27–40 months).
[c] Overall study period was a median of 36 months (interquartile range of 30–43 months).
Source: ISE-PMO Table 14e-1.1; CSR 337 Table 14-1.1; CSR 142 Table 14-1.1; Supplemental CSR 142 Table 7-1; Supplemental CSR 337 Table 7-1, and Table 14r-2.1.501

6.4.7 Efficacy Results for Study 337

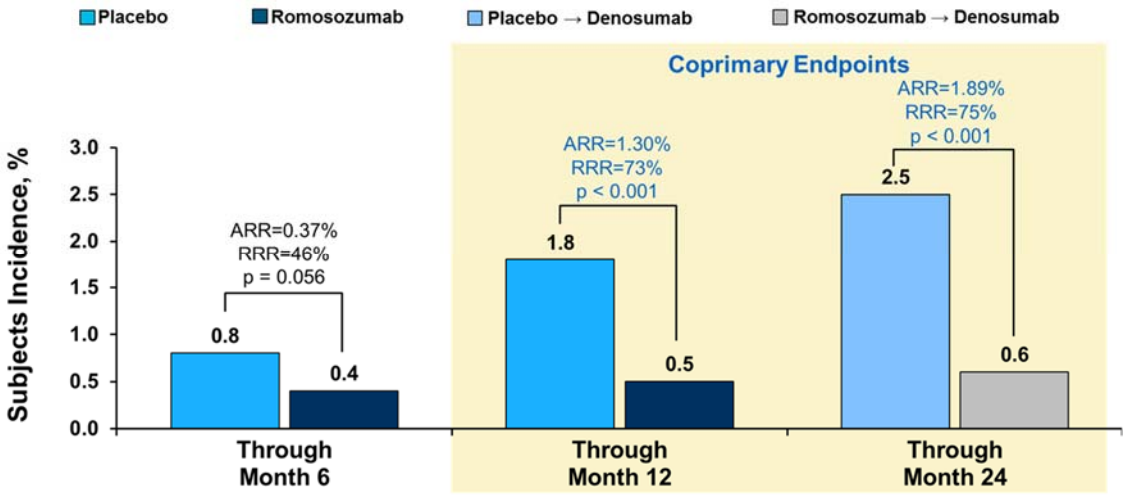
6.4.7.1 Coprimary Endpoints

The coprimary endpoints in Study 337 were subject incidence of new vertebral fracture through 12 months and through 24 months, both were statistically significant:

- Through month 12, romosozumab resulted in a 73% relative risk reduction of new vertebral fracture compared with placebo (absolutely risk reduction [ARR] [95% CI], 1.30% [0.79, 1.80]; p < 0.001), with fractures occurring in 16 of 3321 subjects (0.5%) in the romosozumab group vs 59 of 3322 (1.8%) in the placebo group (Figure 13).
- Through month 24, romosozumab followed by denosumab resulted in a 75% relative risk reduction compared to placebo followed by denosumab (ARR, 1.89% [1.30, 2.49]; p < 0.001), with fractures occurring in 21 of 3325 subjects (0.6%) in the romosozumab→denosumab group vs 84 of 3327 subjects (2.5%) in the placebo→denosumab group (Figure 13).

An exploratory endpoint of new vertebral fracture through month 6 showed that there was a trend for effect on fracture risk as early as month 6 (46% relative risk reduction; p= 0.056) (Figure 13).

Figure 13. Subject Incidence of New Vertebral Fracture Through Month 24 (Study 337)



Absolute risk reduction and risk ratio are based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture stratification variables.
P-values are based on separate logistic regression models adjusting for age and prevalent vertebral fracture stratification variables.
Positive values for absolute risk reduction and values < 1 for risk ratio favor romosozumab.
Source: CSR 337

6.4.7.2 Key Secondary Fracture Endpoints

Romosozumab significantly reduced the risk of clinical fracture (nonvertebral and clinical [ie, symptomatic] vertebral fracture) by 36% (95% CI: 11, 54) compared with placebo through month 12 (ARR, 0.9% [0.2, 1.5]; p = 0.008). Results for key secondary

endpoints are provided in Table 5. The cumulative Incidence of clinical fractures, nonvertebral fractures, and hip fractures through month 24 are shown in Figure 14.

Table 5. Effect of Romosozumab on the Risk of New Vertebral Fractures, Clinical Fractures, Nonvertebral Fractures, and Hip Fractures in Study 337

Time Point Fracture Category	Subjects with Fracture (n/N1 [%])[a]		Absolute Risk Reduction (%), (95% CI)[b]	Relative Risk Reduction (%), (95% CI)[c]	p-value
Study 337	Placebo	Romosozumab 210 mg QM			
Month 12					
New vertebral fracture	59/3322 (1.8)	16/3321 (0.5)	1.3 (0.8, 1.8)	73 (53, 84)	< 0.001
Clinical fracture	90/3591 (2.5)	58/3589 (1.6)	0.9 (0.2, 1.5)	36 (11, 54)	0.008
Nonvertebral fracture	75/3591 (2.1)	56/3589 (1.6)	0.5 (-0.1, 1.1)	25 (-5, 47)	0.096
Hip fracture	13/3591 (0.4)	7/3589 (0.2)	0.2 (-0.1, 0.4)	46 (-35, 78)	0.18 [d]
Month 24					
New vertebral fracture	84/3327 (2.5)	21/3325 (0.6)	1.9 (1.3, 2.5)	75 (60, 84)	< 0.001
Clinical fracture	147/3591 (4.1)	99/3589 (2.8)	1.3 (0.5, 2.2)	33 (13, 48)	0.002 [d]
Nonvertebral fracture	129/3591 (3.6)	96/3589 (2.7)	0.9 (0.1, 1.7)	25 (3, 43)	0.029 [d]
Hip fracture	22/3591 (0.6)	11/3589 (0.3)	0.3 (0.0, 0.6)	50 (-4, 76)	0.059 [d]

n = number of subjects experiencing a fracture; N1 = number of subjects in the primary analysis set for new vertebral fractures (for other fracture endpoints, N1 = N)

[a] Values represent percentage of subjects with fracture in the romosozumab group and the placebo group through month 12, and in the romosozumab→denosumab group and the placebo→denosumab group through month 24.

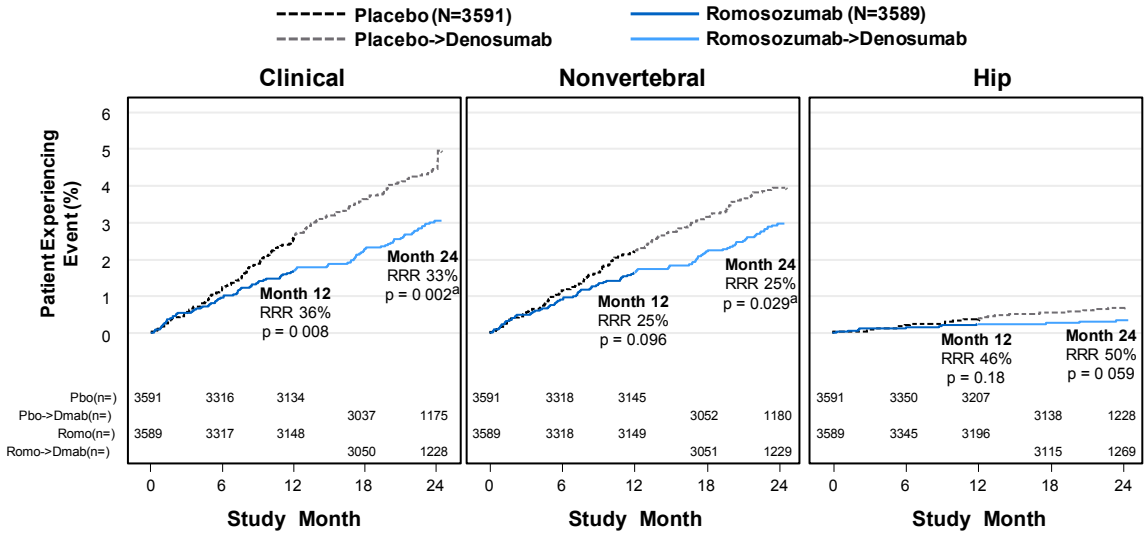
[b] Absolute risk reduction is based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture strata.

[c] Relative risk reduction is based on odds ratio from logistic regression model (new vertrebral frature) and hazard ratio from Cox proportional hazards model (other fracture endpoints) adjusting for age and prevalent vertebrtal fracture strata.

[d] Nominal p-value is not multiplicity adjusted

Source: ISE Table 14r-4.1.502

Figure 14. Time to First Clinical, Nonvertebral, and Hip Fracture Through Month 24; Kaplan-Meier Curves (Study 337)



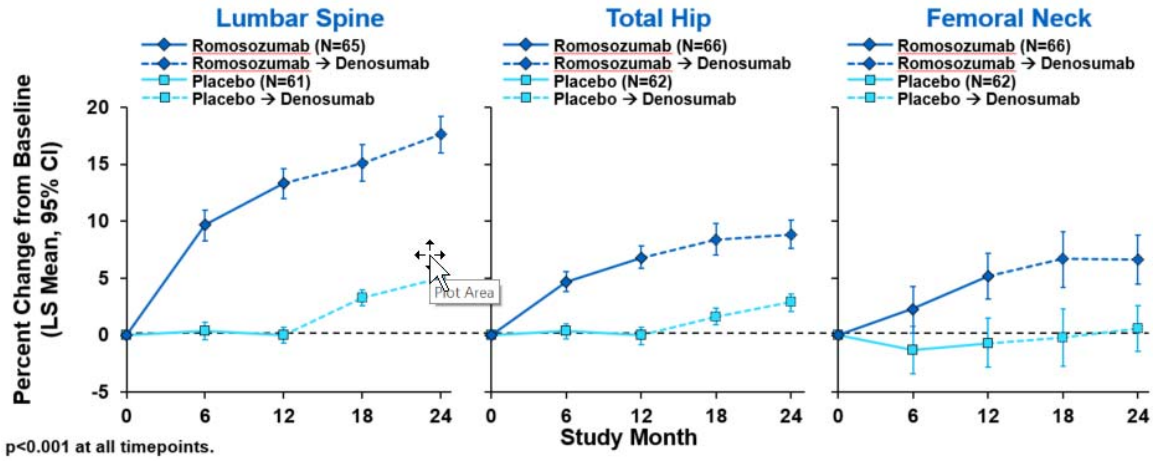
[a] P-value does not meet multiplicity-adjusted statistical significance.
Dmab = denosumab; Pbo = placebo; n = number of subjects at risk for event at time point of interest; Romo = romosozumab
Source: BD, Figure 14z-4.1.1

6.4.7.3 Bone Mineral Density

In Study 337, romosozumab significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with placebo at month 12 (Figure 15). At the lumbar spine, 92.4% of romosozumab-treated subjects gained at least 5% in BMD from baseline at month 12 (compared with 9.3% of subjects in the placebo group), and 68.4% gained 10% or more (compared with 0.9% of subjects in the placebo group). At the total hip, 58.0% of romosozumab-treated subjects gained at least 5% in BMD from baseline at month 12 vs 5.6% with placebo.

Romosozumab followed by denosumab resulted in continued increases in BMD at the lumbar spine, total hip, and femoral neck through month 24, maintaining gains in BMD compared with women who transitioned from placebo to denosumab. Percent change from baseline in BMD at month 24 was significantly greater for subjects in the romosozumab/ denosumab group compared with the placebo/denosumab group (Figure 15).

Figure 15. Percent Change From Baseline in BMD at Lumbar Spine, Total Hip, and Femoral Neck Over 24 Months (Study 337)



ANCOVA = analysis of covariance; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; N = Number of randomized subjects enrolled in the lumbar spine and proximal femur DXA substudy with values at baseline and at least 1 post-baseline visit

Point estimates, 95% confidence intervals, and p-values are based on ANCOVA model adjusting for treatment, baseline value, machine type, and baseline-by-machine type interaction. P-value is for difference in treatment effect.

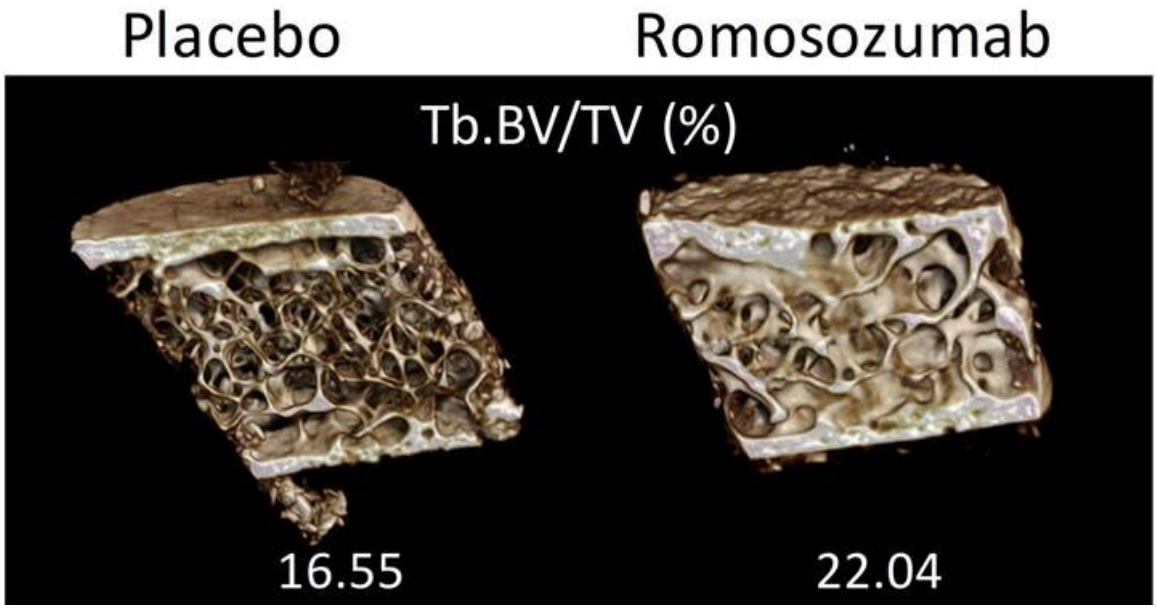
Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the study period.

Source: CO Resub

6.4.7.4 Exploratory or Substudy Endpoints

Micro computed tomography (CT) images of transiliac bone biopsies at month 12 from Study 337 show increased bone volume and trabecular thickness and decreased trabecular bone pattern factor at 12 months with romosozumab (Figure 16).

Figure 16. MicroCT Images at Month 12 From Study 337 Bone Biopsy



	Month 12		
MicroCT	Placebo n = 32	Romosozumab 210 mg QM n = 39	p-value[a]
Tb.BV/TV (%)	15.97 (13.92, 21.13)	22.04 (17.92, 28.61)	0.006
Tb.Th (mm)	0.204 (0.180, 0.232)	0.241 (0.215, 0.293)	0.001
TBPf (/mm)	3.99 (3.25, 5.61)	3.24 (2.11, 4.34)	0.030
Ct.Th (mm)	0.661 (0.535, 0.837)	0.786 (0.621, 0.977)	0.056

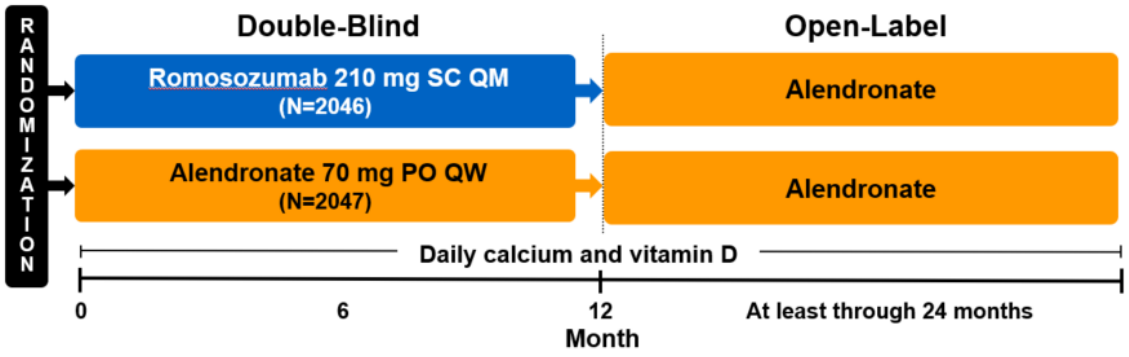
Ct.Th = cortical thickness; Tb.Th=trabecular thickness; Tb.BV/TV=trabecular bone volume per tissue volume; TBPf=trabecular bone pattern factor. Values are median (Q1,Q3).
[a] Wilcoxon rank sum test.
Source: Data on file, Study 337 bone biopsy; Chavassieux et al, 2018.

6.5 Phase 3 Pivotal Study 142

6.5.1 Study Design

Similar to Study 337, pivotal fracture Study 142 evaluated sequential therapy with one year of romosozumab treatment followed by antiresorptive therapy. For Study 142, the antiresorptive agent was alendronate. The study design for Study 142 is shown in Figure 17.

Figure 17. Study Design of Study 142



6.5.2 Enrollment Criteria

Active-controlled Study 142 enrolled a population of postmenopausal women at high risk for osteoporosis-related fracture who have had a prior fracture. Subjects in this study met at least 1 of the following BMD and fracture criteria at study enrollment:

- BMD T-score ≤ -2.5 at the total hip or femoral neck and EITHER at least 1 moderate or severe vertebral fracture OR at least 2 mild vertebral fractures, or
- BMD T-score ≤ -2.0 at the total hip or femoral neck and EITHER at least 2 moderate or severe vertebral fractures OR a fracture of the proximal femur that occurred within 3 to 24 months prior to randomization

6.5.3 Efficacy Endpoints

The primary endpoints in Study 142 were:

- subject incidence of new vertebral fracture through 24 months (romosozumab followed by alendronate vs alendronate alone) and
- subject incidence of clinical fracture through the primary analysis (romosozumab/alendronate vs alendronate alone), which occurred after at least 330 subjects had a clinical fracture and all subjects had the opportunity to complete the month 24 visit. The median follow-up time for study participants when the primary analysis occurred was 33 months (range 0 to 56 months).

Secondary endpoints that were part of the sequential testing sequence were BMD at various time points and anatomical sites, followed by nonvertebral fracture at primary analysis (see Figure 33 for the sequential testing sequence).

The term “nominal” is used for p-values < 0.05 calculated from statistical tests without adjusting for multiplicity.

6.5.4 Statistical Methodology

The statistical methods used in Study 142 were similar to those used in Study 337 (see Section 6.4.4).

6.5.5 Demographics and Baseline Characteristics

The alendronate-controlled fracture Study 142 enrolled patients with a history of fracture and no lower limit for BMD. These women were at higher risk for fracture than those in Study 337 (Appendix 6 compares enrollment criteria). A total of 96% of subjects in Study 142 had at least 1 verified prevalent vertebral fracture at baseline and 38% of subjects had a history of nonvertebral fracture at or after age 45 (Table 3). Subjects in Study 142 were older on average (mean age 74.3 years, with 52.4% of subjects ≥ 75 years) than subjects in Study 337 (mean age 70.9 years, with 31.2% of subjects ≥ 75 years).

More than half of randomized subjects were white. Mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were generally lower in Study 142 than in Study 337 (Table 3). Due to prespecified exclusion criteria and washout periods, a minority of subjects (< 10%) had used osteoporosis treatment medications before enrollment. Baseline characteristics were similar between treatment groups.

6.5.6 Subject Disposition

As in Study 337, about 89% of subjects in Study 142 completed the 12-month double-blind treatment period (Table 4). The most frequent reason for discontinuation

was withdrawn consent. The number and percent of subjects who discontinued the study at later time periods are provided in Table 4.

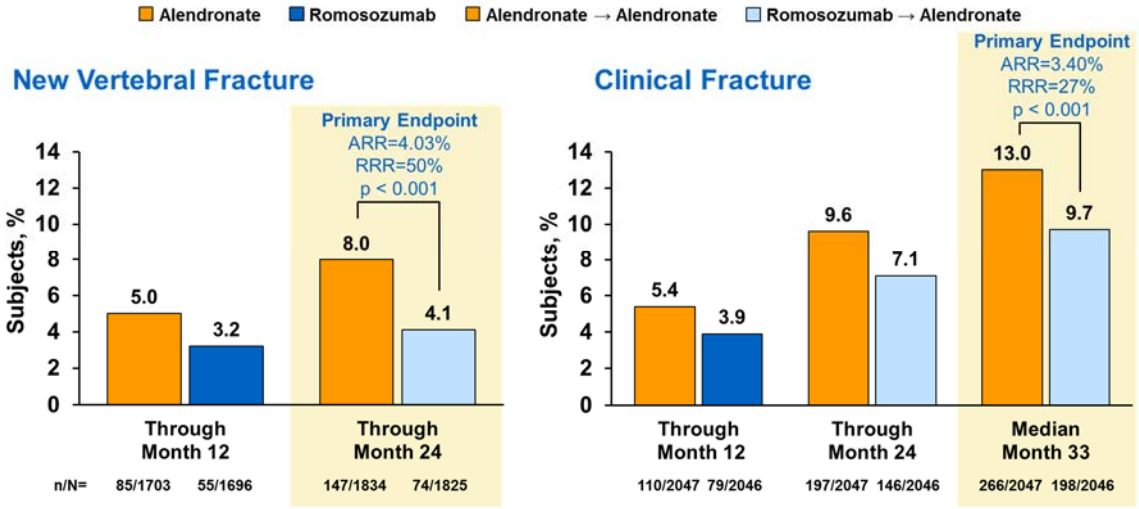
6.5.7 Efficacy Results for Study 142

6.5.7.1 Primary Endpoints

The primary endpoints in Study 142 were new vertebral fractures through 24 months and clinical fractures through primary analysis. Sequential therapy with romosozumab followed by alendronate was superior to alendronate alone in reducing new vertebral fractures and clinical fractures, primary endpoints:

- Through 24 months, sequential treatment with romosozumab followed by alendronate resulted in 50% relative risk reduction of new vertebral fractures (ARR, 4.03% [95% CI: 2.50, 5.57]; p < 0.001), with fractures occurring in 74 of 1825 subjects (4.1%) in the romosozumab→alendronate group vs 147 of 1834 subjects (8.0%) in the alendronate→alendronate group (Table 6, Figure 18).
- Through primary analysis, sequential therapy with romosozumab followed by alendronate resulted in a 27% relative risk reduction of clinical fractures (ARR, 3.40% [95% CI: 1.40, 5.30]; p < 0.001), with fractures occurring in 198 of 2046 subjects (9.7%) in the romosozumab→alendronate group vs 266 of 2047 subjects (13.0%) in the alendronate→alendronate group (Table 6, Figure 18).

Figure 18. Primary Efficacy: Effect of Romosozumab on Incidence of New Vertebral Fractures Through Month 24 and Clinical Fractures Through Month 33 (Study 142)



For new vertebral fracture, absolute (ARR) and relative risk reduction (RRR) is based on Mantel-Haenszel method adjusting for baseline age strata, total hip BMD T-score, and presence of severe vertebral fracture. For clinical fractures, RRR is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline and ARR is based on Mantel-Haenszel method adjusting for baseline age strata, total hip BMD T-score, and presence of severe vertebral fracture.
P-values are based on separate logistic regression models adjusted for age strata, baseline total hip BMD T-score, and the presence of severe vertebral fracture at baseline.
Source: SCE figure 14-4.1.5

6.5.7.2 Key Secondary Fracture Endpoints

Secondary endpoints that were part of the sequential testing sequence were BMD at various time points and anatomical sites, followed by nonvertebral fracture at primary analysis (see Figure 33 for the sequential testing sequence).

At primary analysis (median of 33 months), all secondary endpoints tested showed significant reductions with romosozumab→alendronate vs alendronate→alendronate ($p < 0.05$). Romosozumab reduced new vertebral fractures, clinical fractures, nonvertebral fractures, and hip fractures vs alendronate as early as 12 months and these risk reductions continued to improve through 24 months and primary analysis when all subjects were receiving alendronate (Table 6).

Kaplan-Meier curves of clinical fractures, nonvertebral fractures, and hip fractures through the primary analysis are shown in Figure 19.

Table 6. Effect of Romosozumab on the Risk of New Vertebral Fractures, Clinical Fractures, Nonvertebral Fractures, and Hip Fractures in Study 142

Time Point Fracture Category	Subjects with Fracture (n/N1 [%])[a]		Absolute Risk Reduction (%), (95% CI)[b]	Relative Risk Reduction (%), (95% CI)[c]	p-value
	Alendronate 70 mg QW	Romosozumab 210 mg QM			
Month 12					
New vertebral fracture	85/1703 (5.0)	55/1696 (3.2)	1.84 (0.51, 3.17)	36 (11, 54)	0.008[d]
Clinical fracture	110/2047 (5.4)	79/2046 (3.9)	1.6 (0.3, 28)	28 (4, 46)	0.027[d]
Nonvertebral fracture	95/2047 (4.6)	70/2046 (3.4)	1.2 (0.0, 2.5)	26 (-1, 46)	0.057[d]
Hip fracture	22/2047 (1.1)	14/2046 (0.7)	0.4 (-0.2, 1.0)	36 (-26, 67)	0.19[d]
	Alendronate → Alendronate 70 mg QW	Romosozumab 210 mg QM → Alendronate 70 mg QW			
Month 24					
New vertebral fracture	147/1834 (8.0)	74/1825 (4.1)	4.03 (2.50, 5.57)	50 (34, 62)	< 0.001
Clinical fracture	197/2047 (9.6)	146/2046 (7.1)	2.5 (0.8, 4.2)	26 (9, 41)	0.005[d]
Nonvertebral fracture	159/2047 (7.8)	129/2046 (6.3)	1.5 (-0.1, 3.0)	19 (-2, 36)	0.074[d]
Hip fracture	43/2047 (2.1)	31/2046 (1.5)	0.6 (-0.2, 1.4)	28 (-15, 54)	0.17[d]
Primary analysis (after median follow-up of 33 months)					
Clinical fracture	266/2047 (13.0)	198/2046 (9.7)	3.4 (1.4, 5.3)	27 (12, 39)	<0.001
Nonvertebral fracture	217/2047 (10.6)	178/2046 (8.7)	1.9 (0.1, 3.7)	19 (1, 34)	0.037
Hip fracture	66/2047 (3.2)	41/2046 (2.0)	1.2 (0.2, 2.2)	38 (8, 58)	0.015[d]

n = number of subjects experiencing a fracture; N1 = number of subjects in the primary analysis set for new vertebral fractures (for other fracture endpoints, N1 = N)

[a] Values represent percentage of subjects with fracture in the romosozumab group and the alendronate group through month 12, and in the romosozumab→alendronate group and the alendronate→alendronate group through month 24 and primary analysis.

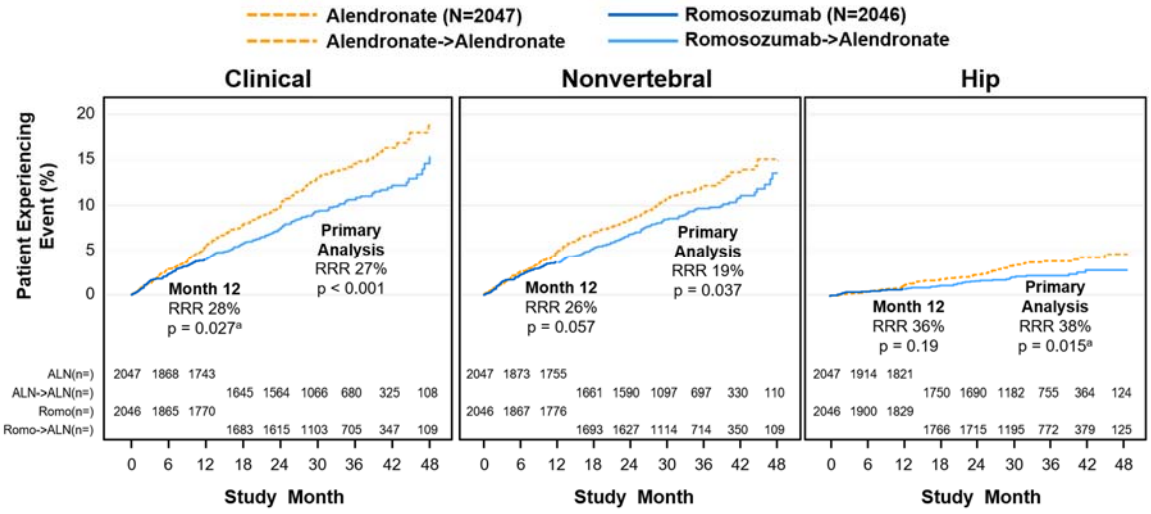
[b] Absolute risk reduction is based on the Mantel-Haenszel method adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.

[c] Relative risk reduction is based on odds ratio from logistic regression model(new vertrebral frature) and hazard ratio from Cox proportional hazards model (other fracture endpoints) adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.

[d] Nominal p-value is not multiplicity adjusted

Source: ISE Table 14r-4.1.501

Figure 19. Time to First Clinical Fracture, Nonvertebral Fracture, and Hip Fracture Through Median Follow-up Time of 33 months; Kaplan-Meier Curves (Study 142)



ALN = alendronate; N = number of subjects randomized; n = number of subjects at risk for event at time point of interest; Romo = romosozumab

[a] Nominal p-value was not multiplicity adjusted
Adjusted p-values are based on a combination of Hochberg, fixed sequential, and group sequential testing procedures for the primary and selected secondary endpoint comparisons.

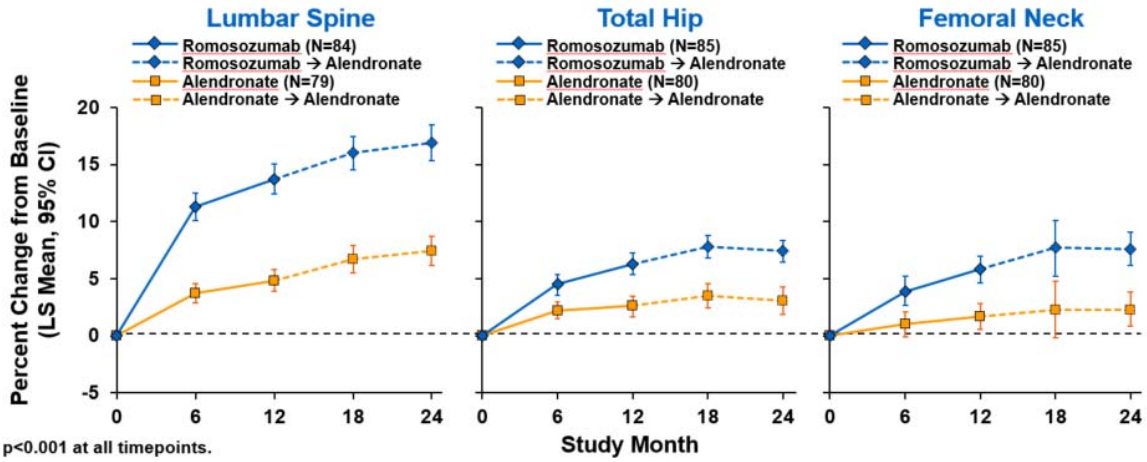
Source: CSE-2, Figure 14-4.1.4

6.5.7.3 Bone Mineral Density

In Study 142, in which the BMD endpoints at months 12 and 24 were included in the testing sequence, romosozumab significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with alendronate at month 12. Romosozumab followed by alendronate significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with alendronate alone at month 24 (Figure 20).

At the lumbar spine, 98.4% of romosozumab-treated subjects gained at least 5% in BMD from baseline at month 12 (compared with 86.7% of subjects in the alendronate group), and 68.2% gained 10% or more (compared with 14.4% of subjects in the alendronate group). At the total hip, 91.1% of romosozumab-treated subjects gained at least 5% in BMD from baseline at month 12 vs 80.2% with alendronate.

Figure 20. Percent Change From Baseline in BMD at Lumbar Spine, Total Hip, and Femoral Neck Over 24 Months (Study 142)



ANCOVA = analysis of covariance; BMD = bone mineral density; PK = pharmacokinetics
N = Number of subjects enrolled in the Imaging and PK/Bone Turnover Marker/Biomarker substudy with values at baseline and at least 1 postbaseline visit at month 6 or month 18.
Point estimates, 95% confidence intervals, and p-values are based on ANCOVA model adjusting for treatment, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. P-value is for difference in treatment effect.
Missing values are imputed by carrying forward the last non-missing postbaseline value prior to the missing value and within the study period.
Source: CO Resub

6.6 Summary of Efficacy

Rapid, marked increases in BMD at the lumbar spine and hip were observed with romosozumab treatment that were clinically meaningful and statistically significantly greater than placebo, teriparatide, and alendronate. These increases were maintained with the transition to antiresorptive therapy.

The gains in BMD translated into fracture risk reduction compared to placebo in Study 337 and alendronate in Study 142. The fracture benefit was seen across multiple fracture endpoints not only through month 12 while subjects were on romosozumab treatment, but continued to increase for at least an additional 12 months after all subjects transitioned to antiresorptive therapy.

Romosozumab's rapid effects of increased skeletal mass, as reflected clinically by greater increases in BMD than comparators, laid the foundation for the greater early fracture risk reduction and maintenance of greater anti-fracture efficacy after transition from romosozumab to antiresorptive agent. Assessment of estimated bone strength by FEA in Study 289 at the spine and hip showed that romosozumab increased trabecular and cortical bone mass. In addition, histomorphometric analyses of bone biopsies from Study 337 showed evidence of an early increase in indices of bone formation and decrease in indices of bone resorption at the tissue level. Improvements in indices of

bone strength, along with increases in skeletal mass and improvements in skeletal microstructure, help explain the robust anti-fracture efficacy that was observed with one year of romosozumab treatment.

7. Overall Safety

7.1 Exposure to Romosozumab

The romosozumab integrated clinical program includes an extensive safety database of approximately 14 000 subjects, of which 7518 subjects received at least 1 dose of romosozumab. Safety evaluations from the pivotal phase 3 fracture studies included:

- 7157 women in Study 337 (3581 received romosozumab)
- 4054 women in Study 142 (2040 received romosozumab)

Safety evaluations from the supportive phase 2 and 3 studies included:

- 432 women in Study 289 (218 received romosozumab)
- 410 women in Study 326 (255 received romosozumab)
- 252 Japanese women in Study 291 (189 received romosozumab)
- 294 women in Study 156 (241 received romosozumab)

Overall, 6180 women received romosozumab for at least 6 months after the first dose and 5712 women received romosozumab for at least 12 months.

In addition, to provide a comprehensive evaluation of CV safety across the pivotal phase 3 studies, CV data from 245 men with osteoporosis who received romosozumab (n = 163) or placebo (n = 82) for up to 12 months (Study 174) are included.

7.2 Overall and Common Adverse Events, Fatal and Serious Adverse Events

In Studies 337 and 142 (n = 11 211), 76% to 80% of subjects across treatment groups had adverse events. The subject incidences of SAEs, adverse events leading to discontinuation, and fatal adverse events were similar between treatment groups in both studies (Table 7).

Table 7. Summary of Subject Incidence of Adverse Events in Studies 337 and 142 (12-month Double-blind Period)

	Study 337		Study 142	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
All adverse events - n (%)	2863 (80.1)	2812 (78.5)	1584 (78.6)	1543 (75.6)
Serious adverse events	314 (8.8)	344 (9.6)	278 (13.8)	262 (12.8)
Leading to discontinuation of investigational product	96 (2.7)	106 (3.0)	66 (3.3)	71 (3.5)
Leading to discontinuation from study	50 (1.4)	45 (1.3)	27 (1.3)	28 (1.4)
Fatal adverse events	24 (0.7)	29 (0.8)	22 (1.1)	30 (1.5)
Treatment-related adverse events - n (%)	496 (13.9)	596 (16.6)	312 (15.5)	300 (14.7)
Serious adverse events	13 (0.4)	16 (0.4)	12 (0.6)	13 (0.6)
Leading to discontinuation of investigational product	48 (1.3)	55 (1.5)	37 (1.8)	27 (1.3)
Leading to discontinuation from study	20 (0.6)	19 (0.5)	13 (0.6)	5 (0.2)
Fatal adverse events	1 (<0.1)	1 (<0.1)	3 (0.1)	0 (0.0)

Source: ISS Table 14r-6.1.1

The most frequently reported adverse events (≥ 10%) were viral upper respiratory tract infection, arthralgia, and back pain in Study 337 and 142 (Table 8).

Table 8. Subject Incidence of Adverse Events in the 12-Month Double-blind Treatment Period in ≥ 5% of Subjects in Any Group (Pivotal Fracture Studies)

	Study 337		Study 142	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
Overall adverse events	2863 (80.1)	2812 (78.5)	1584 (78.6)	1543 (75.6)
Viral URTI	580 (16.2)	573 (16.0)	233 (11.6)	217 (10.6)
Arthralgia	434 (12.1)	468 (13.1)	194 (9.6)	166 (8.1)
Back pain	381 (10.7)	375 (10.5)	228 (11.3)	185 (9.1)
Pain in extremity	299 (8.4)	278 (7.8)	131 (6.5)	121 (5.9)
Fall	320 (8.9)	255 (7.1)	154 (7.6)	129 (6.3)
Headache	208 (5.8)	235 (6.6)	110 (5.5)	106 (5.2)
Hypertension	265 (7.4)	226 (6.3)	132 (6.6)	114 (5.6)
Osteoarthritis	221 (6.2)	189 (5.3)	113 (5.6)	116 (5.7)
URTI	172 (4.8)	161 (4.5)	132 (6.6)	130 (6.4)
Urinary tract infection	147 (4.1)	133 (3.7)	134 (6.7)	104 (5.1)

URTI = upper respiratory tract infection
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 20.0. *Source: ISS Table 14r-6.2.1*

In Studies 337 and 142, The incidence of SAEs was comparable between the treatment groups in both studies (Appendix 5). SAEs were reported more frequently in Study 142 (12.8% romosozumab; 13.8% alendronate) than in Study 337 (9.6% romosozumab; 8.8% placebo), likely due to the enrollment of older subjects in Study 142. Pneumonia was the most frequently reported SAE during the double-blind treatment in both studies, followed by femur fracture. In Studies 337 and 142, fatal adverse events (preferred terms) reported for more than 2 subjects in either treatment group were death, lung neoplasm malignant, acute MI, cerebrovascular accident, pneumonia, and sudden death (Appendix 4). See Section 8 for a full assessment of CV safety.

7.3 Adverse Events of Interest

Comprehensive search strategies of adverse events were used to evaluate events of interest, which included hypocalcemia, hypersensitivity, injection site reactions, malignant or unspecified tumors, hyperostosis, osteoarthritis, atypical femor fracture (AFF) and osteonecrosis of the jaw (ONJ) (Table 9).

Key safety risks:

- **Hypersensitivity:** Like other monoclonal antibodies, romosozumab could be associated with hypersensitivity reactions. Serious hypersensitivity events, while uncommon, occurred at a higher rate in the romosozumab group in Study 337 (0.2% vs 0%) (Table 9). Based on medical review of the safety data, clinically significant hypersensitivity reactions, including dermatitis, rash, angioedema, erythema multiforme and urticaria, are associated with romosozumab. No anaphylactic reactions were reported that were attributable to romosozumab.
- **Hypocalcemia:** Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium. Across the phase 2 and 3 studies, mild and transitory decreases in albumin-corrected calcium (median nadir observed by month 1) and a compensatory increase in intact parathyroid hormone (iPTH) were observed after initiation of romosozumab. The subject incidence of albumin-corrected serum calcium below the central laboratory lower limit of normal was 0.2% with romosozumab and none of these subjects reported adverse events consistent with severe symptomatic hypocalcemia. Based on the totality of data, the risk of hypocalcemia is to be managed with calcium and vitamin D supplementation and appropriate monitoring is recommended for patients with stage 4 or stage 5 chronic kidney disease (CKD). No dose adjustment is needed in patients with renal impairment.
- **Osteonecrosis of the Jaw (ONJ):** ONJ is a known risk observed with antiresorptive agents. As romosozumab has antiresorptive activity, ONJ was adjudicated in the program. The number of positively-adjudicated ONJ cases observed was low and causality was not established. ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. Osteonecrosis of the jaw was reported in 2 subjects in Study 337 (one in month 13 after a single dose of denosumab, and the other one in month 12 after completion of romosozumab). In Study 142, ONJ was reported in 3 subjects, all during the open-label alendronate phase; time to onset ranged from 22 to 56 months.
- **Atypical Femoral Fracture (AFF)**: AFF is a known risk with other antiresorptive agents. As romosozumab has antiresportive activity, AFF was adjudicated in the program. A low number of positively-adjudicated AFF cases was observed and causality was not established. In Study 337, 1 case occurred in a subject in the romosozumab group with confounding factors during the double-blind phase with time to onset of 101 days after initiation of study drug. In Study 142, 7 cases (3 in the romosozumab group and 4 in the control) of AFF occurred during the open-label alendronate phase, with time to onset of 17 to 45 months after initiation of study drug.

Table 9. Summary of Adverse Events of Interest and Adjudicated Adverse Events in 12-Month Double-blind Treatment Period (Pivotal Fracture Studies)

	Study 337		Study 142	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
Hypocalcemia				
Adverse events	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersensitivity				
Adverse events	247 (6.9)	242 (6.8)	118 (5.9)	122 (6.0)
SAEs	0 (0.0)	6 (0.2)	2 (<0.1)	3 (0.1)
Injection site reaction				
Adverse events	104 (2.9)	188 (5.2)	53 (2.6)	90 (4.4)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumors				
Adverse events	55 (1.5)	50 (1.4)	28 (1.4)	32 (1.6)
SAEs	41 (1.1)	35 (1.0)	20 (1.0)	25 (1.2)
Hyperostosis				
Adverse events	28 (0.8)	18 (0.5)	12 (0.6)	2 (<0.1)
SAEs	5 (0.1)	1 (<0.1)	2 (<0.1)	0 (0.0)
Osteoarthritis				
Adverse events	318 (8.9)	285 (8.0)	148 (7.3)	138 (6.8)
SAEs	17 (0.5)	7 (0.2)	6 (0.3)	8 (0.4)
Adjudicated positive AFF				
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Adjudicated positive ONJ				
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AFF = atypical femoral fracture; ONJ = osteonecrosis of the jaw
Hypersensitivity and malignancy include only adverse events as a result of a narrow search/scope in standardized MedDRA queries (SMQ). Hypocalcemia, injection site reaction, hyperostosis, and osteoarthritis include only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies. Preferred terms are coded using MedDRA version 20.0.
Source: CO Resub

7.4 Special Populations

Subjects ≥ Age 65

A subgroup analysis of adverse events by age groups (< 65 years, ≥ 65 years to 74 years, ≥ 75 years to 84 years, and ≥ 85 years) in Studies 337 and 142 did not indicate an altered safety profile of romosozumab by age subgroup. The overall subject incidence of adverse events and the most frequently reported events were similar across age subgroups and between the romosozumab and control groups.

Hepatic Impairment

As a monoclonal antibody, romosozumab is not eliminated via hepatic metabolic mechanisms (eg, by cytochrome P450 [CYP] enzymes). As such, hepatic impairment and drug interaction studies were not necessary and were not conducted.

Renal Impairment

In the phase 1 single dose administration Study 227, which was conducted in 8 healthy subjects and 8 subjects each with stage 4 CKD or stage 5 CKD (the latter receiving hemodialysis), the administration of romosozumab resulted in a greater decrease in serum calcium level and a greater compensatory physiological increase in iPTH in subjects with stage 4 CKD and stage 5 CKD receiving hemodialysis than in healthy subjects. Most of these changes were transient and returned to baseline by the end of the study. Management with calcium and vitamin D supplementation and appropriate monitoring is recommended for patients with stage 4 or 5 kidney disease as outlined above for hypocalcemia.

7.5 Immunogenicity and Impact on PK, Safety, and Efficacy

The incidence of developing binding and neutralizing anti-romosozumab antibodies in women who received romosozumab 210 mg monthly was 18.1% (1072 of 5914) and 0.8% (50 of 5914), respectively.

Based on mean values, the presence of binding anti-romosozumab antibodies appeared to decrease romosozumab exposure up to 19% at months 3, 6, and 9. The exposures became comparable (less than 10% difference in mean values) at month 12 between antibody positive and antibody negative subjects.

Mean percent change from baseline BMD was not impacted by antibody status. Similar values were observed at hip, lumbar spine, and femoral neck for binding antibody negative, binding antibody positive, and neutralizing antibody positive subjects. No evidence of an association of hypersensitivity, injection site reactions, or autoimmune

disorders with binding or neutralizing anti-romosozumab antibodies was noted. Therefore, there is no evidence that anti-romosozumab antibodies impact the efficacy or safety of romosozumab.

7.6 Summary of Non-Cardiovascular Overall Safety

Key risks with romosozumab include hypersensitivity, hypocalcemia, ONJ, and AFF.

As with other monoclonal antibodies, hypersensitivity reactions were observed with romosozumab administration. Based upon the mechanism of action of building bone, decreases in serum calcium were observed and did not lead to clinical sequelae. Rare cases of ONJ and AFF were observed in the clinical program.

8. Cardiovascular Safety Assessment

Prior to the initiation of phase 3 Studies 337, 142, and 174, there was no evidence of an increased CV risk based on treatment-emergent adverse events in the 12 phase 1, 2 phase 2, and 2 phase 3 studies completed at the time of the End of Phase 2 meeting. No alteration in CV risk factors, such as blood pressure, glucose control, or lipids, was observed and potential CV events were not adjudicated.

Due to an external nonclinical study reporting that sclerostin is upregulated in areas of vascular calcification and may be an inhibitor of vascular calcification (Zhu et al, 2011), prospective, independent, treatment-blinded, central adjudication of cardiovascular serious adverse events (CV SAEs) was added to 3 pivotal phase 3 protocols (Studies 337 and 142 in women with PMO, and Study 174 in men with osteoporosis).

No imbalance in positively-adjudicated CV SAEs was observed in placebo-controlled Study 337 at month 12 or in the overall study period. In the alendronate-controlled Study 142, more subjects on romosozumab experienced MACE events (CV death, MI, and stroke) than on alendronate at month 12. This was driven by infrequent incidences of MI and stroke during the 12-month double-blind period. This imbalance diminished during the overall study period although the difference in stroke remained. A numerical imbalance in positively-adjudicated CV SAEs was observed in the male osteoporosis Study 174; however, too few events occurred to contribute meaningfully to the CV safety assessment.

8.1 Methods for Assessment and Adjudication of Cardiovascular Adverse Events

Adjudication in the pivotal phase 3 studies (Studies 337, 142, and 174) was performed by Duke Clinical Research Institute (DCRI) using the Clinical Data Interchange Standards Consortium definitions (Hicks et al, 2014). All deaths, SAEs meeting prespecified “trigger” MedDRA preferred terms (from a list of approximately 500 CV-related terms), and additional SAEs identified by DCRI were adjudicated. Investigators were permitted to submit other CV SAEs for adjudication. The DCRI adjudication committee was blinded to treatment assignment throughout the adjudication process and the duration of the studies.

The prespecified endpoint for the DCRI adjudication was the subject incidence of positively-adjudicated CV SAEs. DCRI positively-adjudicated 697 CV SAEs from the 1150 SAEs that were identified for adjudication (Table 10). The subject incidence of positively-adjudicated CV SAEs was summarized according to event classifications in

the DCRI charter as follows: death, cardiac ischemic events (MI, angina), cerebrovascular events (stroke, transient ischemic attack), noncoronary revascularization, hospitalization for heart failure, and peripheral vascular event not requiring revascularization. Positively-adjudicated CV death included CV death and death of undetermined cause. Results of the CV adjudication by DCRI are provided beginning in Section 8.4.

A priori, an imbalance in CV SAEs was not expected given the totality of clinical and nonclinical romosozumab data accumulated prior to institution of central CV adjudication. Adjudication by DCRI was based on serious adverse events that met prespecified CV-related event terms, focusing the scope of the adjudication. However, when the imbalance was detected in Study 142, the Sponsor felt it critical to perform a comprehensive review of all available data from Studies 337, 142, and 174. A second independent central adjudication process was conducted by the Thrombolysis In Myocardial Infarction (TIMI) Study Group.

TIMI considered all adverse events, irrespective of seriousness, to ensure that all CV events were identified and adjudicated. Their independent post hoc review included readjudication of all deaths and other serious adverse events previously adjudicated by DCRI. This process was blinded to treatment assignment and DCRI adjudication result. TIMI reviewed 80 214 adverse events, both nonserious and serious, and positively-adjudicated 690 CV SAEs (Table 10). The comprehensive review and adjudication by TIMI did not provide more events; the total number of events adjudicated as positive was 697 with DCRI and 690 with TIMI (Table 10). Results based on adjudication by TIMI were consistent with the results of the adjudication by DCRI, as demonstrated by a similar number of subjects who experienced MI, stroke, and CV death in the studies (Appendix 7). Since the DCRI and TIMI results and conclusions were similar, Amgen focused on the prespecified DCRI results in this document; in consultation with FDA, agreement was reached on this approach.

Table 10. Number of Events Adjudicated Across Studies 337, 142, and 174 (DCRI and TIMI)

	DCRI Adjudication		TIMI Adjudication	
	12-Month Double Blind Period	Overall Study Period	12-Month Double Blind Period	Overall Study Period
Number of adverse events eligible for adjudication[a]	1757	5070	42273	80214
Total number sent for adjudication	359	1150	431	1329
Outcome of adjudication				
Number positively adjudicated	210	697	206	690
Number negatively adjudicated	149	453	195	577

An event is considered positively-adjudicated if the adjudication result is positive for any pre-specified cardiovascular category.
[a] DCRI only adjudicated serious adverse events and TIMI reviewed all events to triage for adjudication regardless of seriousness
Source: Table 14z-1.1, Table 14z-1.2, and CV report Table 14-1.1, Table 14-1.2

8.2 Cardiovascular Disposition

In the 2 pivotal fracture studies in postmenopausal women with osteoporosis, approximately 10% of subjects discontinued study in the first year (Appendix 8). Among these, 0.6% of subjects in Study 337 and 1% of subjects in Study 142 had at least one positively-adjudicated CV SAE and contributed to the 12-month double-blind period evaluation of CV safety. In the overall study period, approximately 20% of Study 337 and 25% of Study 142 discontinued study prior to study completion. Among these, 1.8% of subjects in Study 337 and 4.3% in Study 142 had at least one positively-adjudicated CV SAE and contributed to the overall study period evaluation of CV safety.

8.3 Baseline Characteristics Including CV-related Medical History

8.3.1 Demographics

Characteristics of the study populations were generally balanced between the treatment groups within each study. The mean age of subjects in Study 142 was 3.5 years older than that of subjects in Study 337 (Table 11).

Table 11. Summary of Key Baseline Characteristics (Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3576)	Romosozumab 210 mg QM (N = 3581)	Alendronate 70 mg QW (N = 2014)	Romosozumab 210 mg QM (N = 2040)
Age (years)				
Mean (SD)	70.8 (6.9)	70.9 (7.0)	74.2 (7.5)	74.4 (7.5)
Age group - n (%)				
< 75 years	2461 (68.8)	2464 (68.8)	965 (47.9)	970 (47.5)
≥ 75 years	1115 (31.2)	1117 (31.2)	1049 (52.1)	1070 (52.5)
Smoking history - n (%)				
Current/former	1037 (29.0)	982 (27.4)	591 (29.3)	533 (26.1)
Creatinine (mg/dL)				
Mean (SD)	0.82 (0.17)	0.83 (0.18)	0.82 (0.19)	0.84 (0.20)
Estimated glomerular filtration rate (mL/min/1.73 m^2)				
Median	71.1	71.1	70.3	69.9
Q1, Q3	61.7, 83.0	61.4, 83.0	60.2, 82.7	59.9, 81.8

eGFR = estimated glomerular filtration rate; Q1 = first quartile; Q3 = third quartile
For Studies 337 and 142, baseline eGFR was reported by the central laboratory.
Source: Modified from Table 14-2.1 of CV report

8.3.2 Cardiovascular-related Medical History

Cardiovascular-related medical history in the clinical studies was collected as part of general medical history; there were no specific prompts or case report forms used. Cardiovascular-related medical history characteristics were generally balanced between the treatment groups within each study. Subjects in Study 142 had more hypertension, coronary artery disease (ischemic heart disease, MI), and cerebrovascular disease (ischemic stroke or transient ischemic attack) than in Study 337 (Table 12).

Table 12. Summary of CV-related Medical History (Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3576)	Romosozumab 210 mg QM (N = 3581)	Alendronate 70 mg QW (N = 2014)	Romosozumab 210 mg QM (N = 2040)
Any CV-related medical history - n (%)	2703 (75.6)	2649 (74.0)	1603 (79.6)	1618 (79.3)
History of:				
Hypercholesterolemia	1408 (39.4)	1379 (38.5)	675 (33.5)	709 (34.8)
Hypertension	1919 (53.7)	1890 (52.8)	1227 (60.9)	1248 (61.2)
Diabetes	472 (13.2)	452 (12.6)	276 (13.7)	245 (12.0)
Ischemic heart disease	343 (9.6)	318 (8.9)	257 (12.8)	295 (14.5)
Cerebrovascular dis.	198 (5.5)	179 (5.0)	186 (9.2)	149 (7.3)
Atrial fib/atrial flutter	76 (2.1)	58 (1.6)	76 (3.8)	93 (4.6)
Stroke	95 (2.7)	83 (2.3)	81 (4.0)	58 (2.8)
Myocardial infarction	77 (2.2)	76 (2.1)	50 (2.5)	71 (3.5)

Atrial fib = atrial fibrillation; MedDRA = Medical Dictionary for Regulatory Activities;
CV medical histories were based on standard MedDRA queries, Amgen MedDRA queries, high-level group terms, or system organ class using MedDRA v 20.
Source: Modified from Table 14-2.1 and Table 14-2.6 of CV report

8.3.3 Baseline Cardiovascular Concomitant Medications

In Studies 337 and 142, the use of CV-related medications at baseline (ie, started on or before study day 1 and continued during the study) was similar between treatment groups within each study (Table 13).

Consistent with the higher prevalence of cardiovascular disease in Study 142, there was greater baseline use of cardiovascular medications, like beta-blockers, ACE inhibitors, and anticoagulants in Study 142 compared with Study 337.

Table 13. CV-related Baseline Concomitant Medications (Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
In all subjects				
Subjects with CV-related baseline medications	2065 (57.7)	2018 (56.4)	1238 (61.5)	1254 (61.5)
Aspirin	713 (19.9)	751 (21.0)	437 (21.7)	449 (22.0)
Antiplatelet therapy	755 (21.1)	801 (22.4)	473 (23.5)	483 (23.7)
Beta-blockers	729 (20.4)	716 (20.0)	478 (23.7)	518 (25.4)
Anticoagulants	815 (22.8)	837 (23.4)	559 (27.8)	578 (28.3)
Angiotensin II receptor antagonists	600 (16.8)	578 (16.1)	374 (18.6)	347 (17.0)
Statins	943 (26.4)	913 (25.5)	476 (23.6)	498 (24.4)
ACE Inhibitors	702 (19.6)	730 (20.4)	490 (24.3)	532 (26.1)
Insulin	64 (1.8)	59 (1.6)	55 (2.7)	40 (2.0)
Non-insulin glycemic control medication	303 (8.5)	291 (8.1)	160 (7.9)	154 (7.5)

ACE = angiotensin-converting enzyme
Baseline concomitant medications include medications started on or before study Day 1 and were ongoing while on study. Medications are coded using WHO Drug Dictionary 2016Q2 for Study 337 and WHO Drug Dictionary 2016Q4 for Study 142.
Source: Table 14-8.4.1 and Table 14-8.3.1 of CV report and Table 14z-8.1.13

8.4 Prespecified CV Serious Adverse Events (Adjudication by DCRI)

While CV adjudication was performed in Studies 337, 142, and 174, Study 174 was conducted in 244 men with osteoporosis and a total of 10 subjects with positively-adjudicated CV SAEs were identified: 8 of 163 subjects (4.9%) in the romosozumab arm vs 2 of 81 subjects (2.5%) in the placebo arm. Compared to Studies 337 and 142 that were conducted in 11 211 women with PMO with a total of 180 subjects with positively-adjudicated CV SAEs in the 12-month double-blind treatment period, Study 174 does not contribute meaningfully to our understanding of the safety of romosozumab in women with PMO. Thus, in consultation with FDA, this document presents data for the 2 pivotal fracture studies in women with PMO (Studies 337 and 142).

12-month double-blind period

Study 337

In Study 337, the subject incidence of positively-adjudicated CV SAEs was the same between the romosozumab and placebo group in the large, placebo-controlled Study 337 (46 [1.3%] subjects in each group, Table 14). The subject incidence for MI (romosozumab, 9 [0.3%] subjects; placebo, 8 [0.2%] subjects), stroke (romosozumab, 8 [0.2%] subjects; placebo, 10 [0.3%] subjects), and CV death (romosozumab, 17 [0.5%] subjects; placebo, 15 [0.4%] subjects) was generally balanced between groups for the 12-month double-blind treatment period (Table 14). The incidence of ischemic stroke was lower with romosozumab (2 [< 0.1%]) than with placebo (10 [0.3%]) in this study.

The subject incidence of heart failure, noncoronary revascularization, and peripheral vascular ischemic events not requiring revascularization was balanced between treatment groups in Study 337 (Table 14).

Study 142

In Study 142, there was a higher subject incidence of positively-adjudicated CV SAEs observed with romosozumab (50 subjects [2.5%]) vs alendronate (38 subjects [1.9%]) during the 12-month double-blind treatment period. The higher incidence was observed for MI (romosozumab, 16 [0.8%] subjects; alendronate, 5 [0.2%] subjects) and for stroke (romosozumab, 13 [0.6%] subjects; alendronate, 7 [0.3%] subjects) (Table 14). The incidence of ischemic stroke was 10 (0.5%) with romosozumab vs 6 (0.3%) with alendronate in Study 142. The incidence of CV death was generally balanced between treatment groups. The subject incidences of heart failure, noncoronary revascularization, and peripheral vascular ischemic events not requiring revascularization were balanced or lower in the romosozumab arm vs alendronate in Study 142 (Table 14).

Table 14. Subject Incidence of Positively-Adjudicated CV SAEs by Category and Study in the 12-month Double-blind Period (DCRI Adjudication of Studies 337 and 142)

	Study 337		Study 142	
Category Subcategory Subtype	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
Number of subjects reporting adjudicated positive CV SAE	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Cardiac ischemic event	**16 (0.4)**	**16 (0.4)**	**6 (0.3)**	**16 (0.8)**
Angina[a]	7 (0.2)	7 (0.2)	1 (<0.1)	0 (0.0)
Myocardial infarction[a]	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Type 1 (spontaneous)	7 (0.2)	8 (0.2)	2 (<0.1)	13 (0.6)
PCI or coronary bypass graft, without MI/angina	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular event	**11 (0.3)**	**10 (0.3)**	**7 (0.3)**	**16 (0.8)**
Stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
Hemorrhagic stroke	0 (0.0)	4 (0.1)	0 (0.0)	3 (0.1)
Ischemic stroke	10 (0.3)	2 (<0.1)	6 (0.3)	10 (0.5)
Undetermined stroke	0 (0.0)	2 (<0.1)	1 (<0.1)	0 (0.0)
Transient Ischemic Attack	1 (<0.1)	2 (<0.1)	0 (0.0)	3 (0.1)
CV Death[b]	**15 (0.4)**	**17 (0.5)**	**12 (0.6)**	**17 (0.8)**
CV-Related	9 (0.3)	6 (0.2)	5 (0.2)	10 (0.5)
Undetermined	6 (0.2)	11 (0.3)	7 (0.3)	7 (0.3)
Heart failure	**5 (0.1)**	**7 (0.2)**	**8 (0.4)**	**4 (0.2)**
Noncoronary revasc	**2 (<0.1)**	**1 (<0.1)**	**5 (0.2)**	**3 (0.1)**
Peripheral vascular ischemic event not requiring revasc	**1 (<0.1)**	**4 (0.1)**	**2 (<0.1)**	**0 (0.0)**

PCI = percutaneous coronary intervention; revasc = revascularization
Events in gray are components of MACE and are discussed separately in Section 8.5.3.
[a] Includes coronary revascularization procedures that may have been performed as part of adjudicated event. Other subtypes of MI (shown in the source table) included Type 2 (secondary), Type 4a (Peri-PCI), and Type 4b (Stent thrombosis).
[b] Includes fatal events adjudicated as CV-related or undetermined
A subject may be counted in more than 1 category/subcategory.
Source: Modified from Table 14-6.2.9 of CV Report

Overall study period

Study 337

In Study 337, the subject incidence of MI was 23 subjects (0.6%) in the romosozumab arm compared with 19 subjects (0.5%) in the placebo arm (Table 15). The incidence of stroke was 37 subjects (1.0%) in the romosozumab arm compared with 31 subjects (0.9%) in the placebo arm in the overall study period. The subject incidence of CV death, heart failure, noncoronary revascularization, and peripheral vascular ischemic events not requiring revascularization was generally balanced between treatment groups in Study 337 (Table 14).

Study 142

In Study 142, the overall study period included the short follow-up period after the primary analysis. In this event-driven study, the overall study period occurred at a median of 36 months (interquartile range of 30-43 months). In the overall study period, the subject incidence of MI was 23 subjects (1.1%) in the romosozumab arm compared with 21 subjects (1.0%) in the alendronate arm (Table 15). The incidence of stroke remained higher in the romosozumab arm (42 [2.1%]) compared with alendronate (24 [1.2%]) in the overall study period. The subject incidence of CV death, heart failure, noncoronary revascularization, and peripheral vascular ischemic events not requiring revascularization was generally balanced between treatment groups in Study 142 (Table 14).

Table 15. Subject Incidence of Positively-Adjudicated CV SAEs by Study in the Overall Study Period (DCRI Adjudication of Studies 337 and 142)

Category Subcategory Subtype	Study 337		Study 142	
	Placebo/ Denosumab 60 mg Q6M (N = 3576) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3581) n (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2040) n (%)
Number of subjects reporting adjudicated positive CV SAEs	124 (3.5)	128 (3.6)	137 (6.8)	144 (7.1)
Cardiac ischemic event	**38 (1.1)**	**36 (1.0)**	**25 (1.2)**	**32 (1.6)**
Angina[a]	17 (0.5)	13 (0.4)	5 (0.2)	8 (0.4)
Myocardial infarction[a]	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Type 1 (spontaneous)	17 (0.5)	20 (0.6)	14 (0.7)	17 (0.8)
PCI or coronary bypass graft, without MI or angina	3 (<0.1)	3 (<0.1)	0 (0.0)	1 (<0.1)
Cerebrovascular event	**36 (1.0)**	**43 (1.2)**	**27 (1.3)**	**47 (2.3)**
Stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
Hemorrhagic stroke	7 (0.2)	9 (0.3)	3 (0.1)	7 (0.3)
Ischemic stroke	23 (0.6)	26 (0.7)	19 (0.9)	33 (1.6)
Undetermined stroke	1 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Transient ischemic attack	5 (0.1)	7 (0.2)	4 (0.2)	5 (0.2)
CV Death[b]	**50 (1.4)**	**43 (1.2)**	**68 (3.4)**	**67 (3.3)**
CV-Related	29 (0.8)	20 (0.6)	27 (1.3)	36 (1.8)
Undetermined	21 (0.6)	23 (0.6)	41 (2.0)	31 (1.5)
Heart failure	**15 (0.4)**	**12 (0.3)**	**25 (1.2)**	**14 (0.7)**
Noncoronary revasc	**4 (0.1)**	**2 (<0.1)**	**10 (0.5)**	**7 (0.3)**
Peripheral vascular ischemic event not requiring revasc	**3 (<0.1)**	**8 (0.2)**	**5 (0.2)**	**2 (<0.1)**

PCI = percutaneous coronary intervention; Q6M = every 6 months; QW = weekly; revasc = revascularization
N = Number of subjects in the safety analysis set; n = Number of subjects reporting ≥ 1 event
Overall study period (ie, through end of study) included follow-on therapy for 2 years in Study 337 and at least 1 year in Study 142 after the 12-month double-blind period.
Events in gray are components of MACE and are discussed separately in Section 8.5.3.
[a] Includes coronary revascularization procedures that may have been performed as part of adjudicated event. Other subtypes of MI (shown in the source table) included Type 2 (secondary), Type 4a (Peri-PCI), and Type 4b (Stent thrombosis).
[b] CV death events include fatal events adjudicated as CV-related or undetermined.
Source: Modified from Table 14-6.2.11 of CV Report

8.5 Time to Event Analyses

Time to event analyses were conducted for all positively-adjudicated CV SAEs, MACE, and the individual components of MACE.

8.5.1 Study 337

In Study 337, in the 12-month double-blind period, the HRs for CV SAEs, MACE, CV death, MI, and stroke were close to 1.0 (left side of Figure 22).

In the overall study period of 36 months, the HRs for CV SAEs, MACE, CV death, MI, and stroke were close to 1.0 (right side of Figure 22).

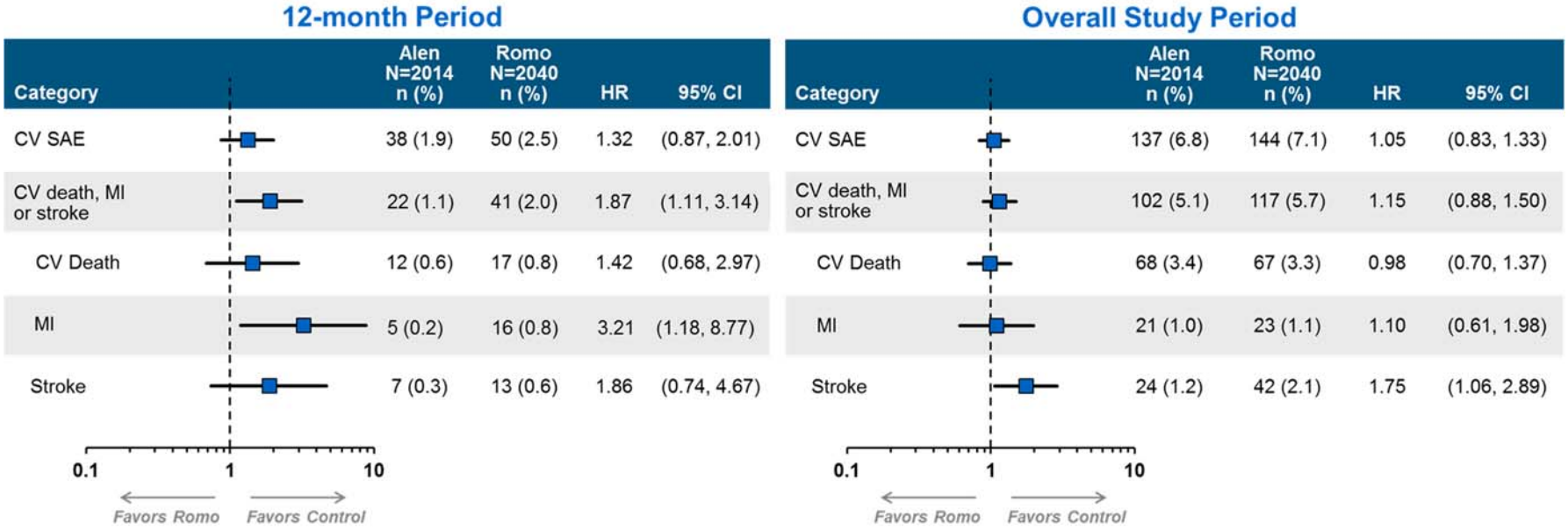
8.5.2 Study 142

For the 12-month double-blind period, the hazard ratio (HR) for the MACE composite for Study 142 was 1.87 (95% CI: 1.11, 3.14), which was primarily driven by an increased incidence of MI and less so by stroke as shown below and in Figure 21.

- MACE Composite: HR of 1.87 (95% CI: 1.11, 3.14) with incidences of 41 (2.0%) for romosozumab vs 22 (1.1%) for alendronate
- MI: HR of 3.21 (95% CI: 1.18, 8.77) with incidences of 16 (0.8%) for romosozumab vs 5 (0.2%) for alendronate
- Stroke: HR of 1.86 (95% CI: 0.74, 4.67) with incidences of 13 (0.6%) for romosozumab vs 7 (0.3%) for alendronate

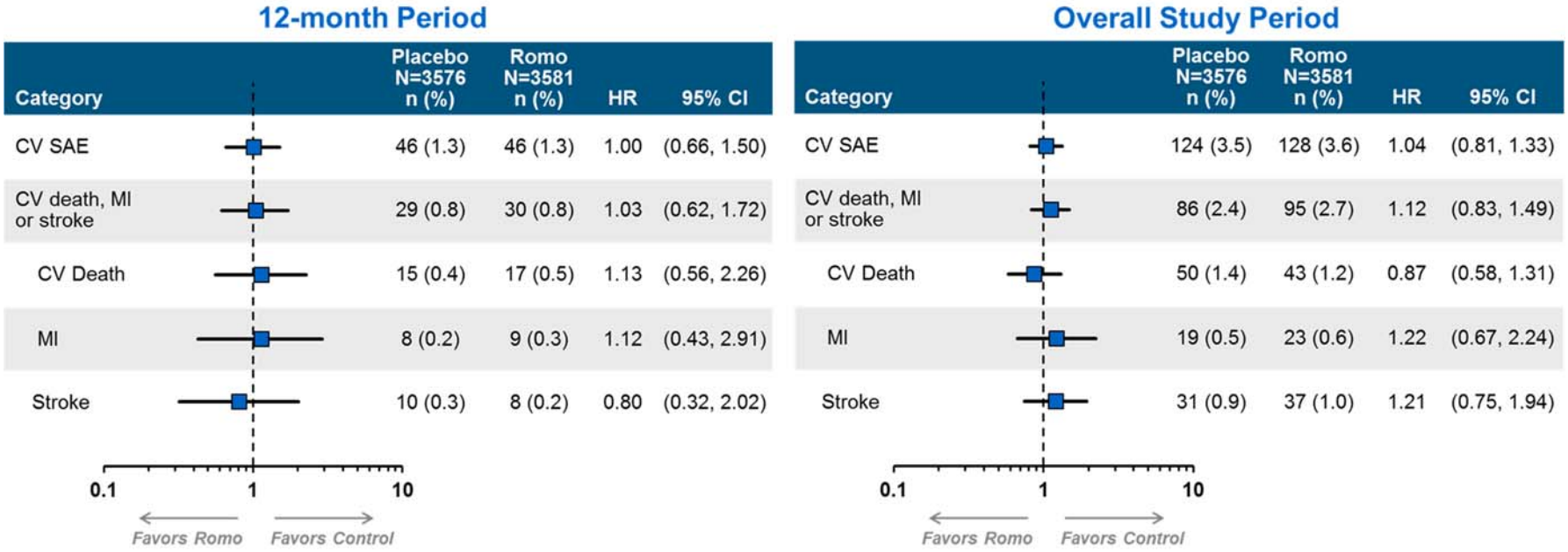
For the overall study period, with a median study duration of 36 months (interquartile range of 30–43 months), all HRs were close to 1.0 except for stroke. During the overall study period, the stroke HR remained elevated (HR of 1.75; 95% CI: 1.06, 2.89) with incidences of 42 (2.1%) on romosozumab/alendronate and 24 (1.2%) on alendronate alone (Figure 21, Table 15).

Figure 21. Time to First Occurrence of Positively-Adjudicated CV SAEs, MACE Composite and Components in the 12-Month Double-blind and Overall Study Periods (DCRI Adjudication of Study 142)



Source: Figures 14z-6.7.2, 14z-6.7.7, 14z-6.5.13, and 14z-6.5.14

Figure 22. Time to First Occurrence of Positively-Adjudicated CV SAEs, MACE Composite and Components in the 12-Month Double-blind and Overall Study Periods (DCRI Adjudication of Study 337)



Source: Figures 14z-6.7.1, 14z-6.7.2, 14z-6.5.13 and 14z-6.5.14

8.5.3 Meta-analyses Across Studies 337 and 142

To evaluate the totality of evidence for cardiovascular events in the PMO population, a meta-analysis of the 2 pivotal fracture studies (Studies 337 and 142) was performed stratified by study. A priori, there was no reason to expect the effect of romosozumab on the incidence of cardiovascular events would differ between these two studies. As each study contributed a modest number of events, it is possible the estimated hazard ratios of CV risk from each study may reflect random high and/or random low bias. Therefore, the estimated hazard ratio from a meta-analysis of the 2 studies may provide a more robust estimate of the true risk of CV events. However, as there is heterogeneity in baseline risk and different comparator arms in each study, the results of the meta-analysis should be interpreted with caution given these limitations.

A meta-analysis was performed for CV SAEs (Section 8.5.3.1) and for MACE (Section 8.5.3.2) with forest plots showing each study separately as well as the meta-analysis result.

8.5.3.1 Positively-adjudicated CV SAEs

The incidence of positively-adjudicated CV SAEs through month 12 across the 2 studies was 1.7% for romosozumab vs 1.5% for control (placebo or alendronate); HR: 1.14 (95% CI: 0.85, 1.53) (Figure 23).

The incidence of positively-adjudicated CV SAEs in the overall study period across both studies was 4.8% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs 4.7% for the control (placebo or alendronate)/antiresorptive therapy (denosumab or alendronate) group; HR: 1.05 (95% CI: 0.88, 1.24) (Figure 23).

8.5.3.2 Composite of CV Death, MI or Stroke (MACE)

A post hoc analysis using the composite endpoint of positively-adjudicated CV death, MI and stroke (MACE) was performed with results below.

12-month double-blind period

The incidence of MACE through month 12 across the 2 studies was 1.3% for romosozumab vs 0.9% for control (placebo or alendronate); HR: 1.39 (95% CI: 0.97, 2.00) (Figure 24). Hazard ratios for CV death and MI were close to 1.0. The HR for stroke was 1.24 (95% CI: 0.65, 2.34) (Figure 25).

Overall study period

The incidence of MACE in the overall study period across the 2 studies was 3.8% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs 3.4% for the

control (placebo or alendronate)/follow-on therapy (denosumab or alendronate) group; HR: 1.13 (95% CI: 0.93, 1.38) (Figure 24). The HRs for the individual studies in the overall study period are shown in Figure 24.

The Kaplan-Meier curves for MACE for the meta-analysis of Studies 337 and 142 are shown in Figure 26 and the individual components of MI and stroke in Studies 337 and 142 are in Figure 27 (for MI) and Figure 28 (for stroke).

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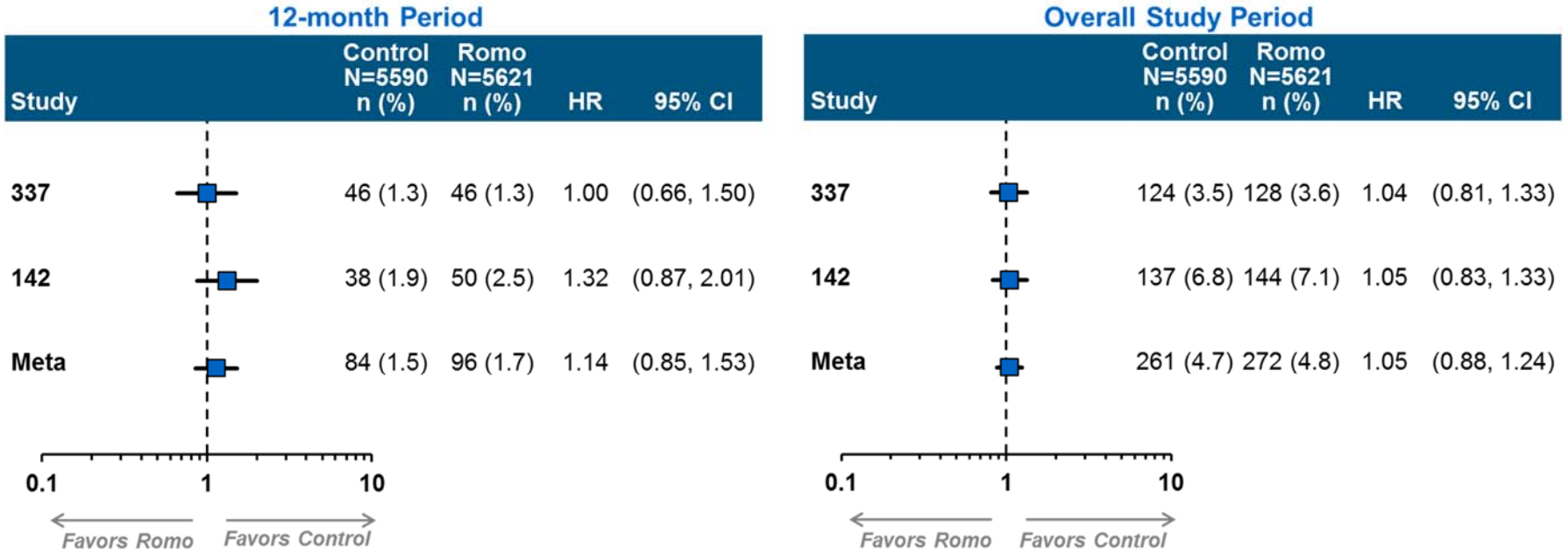
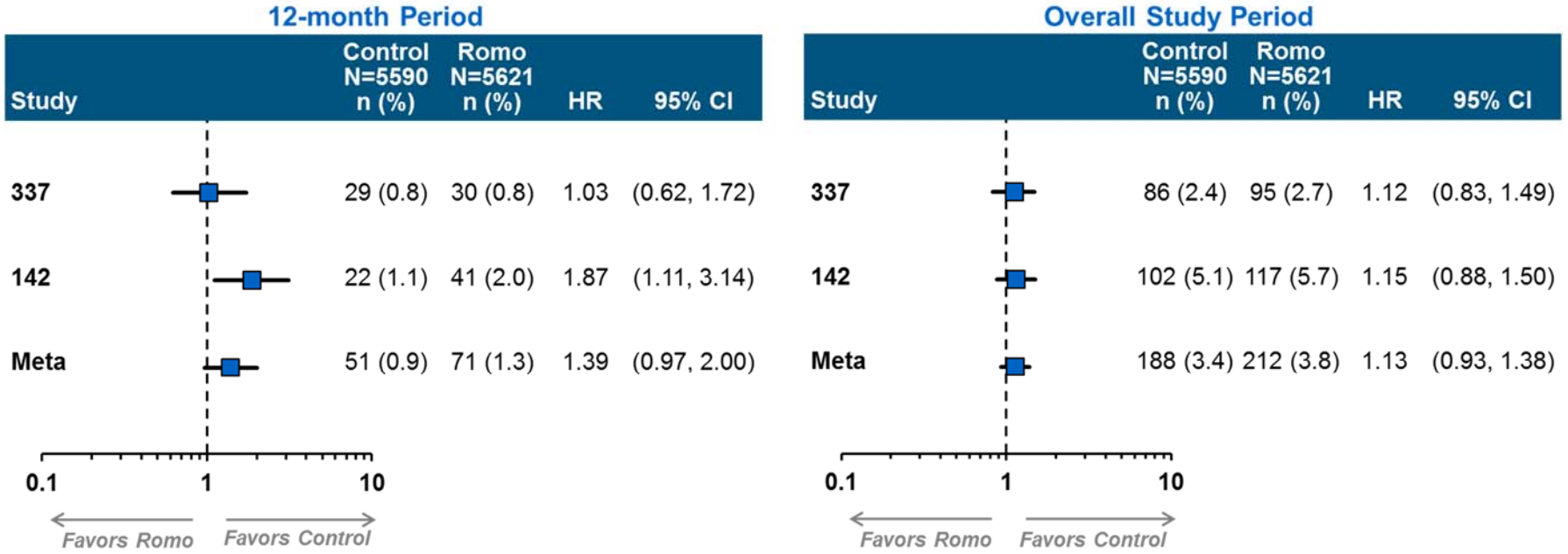
Figure 23. Time to First Occurrence of Positively-Adjudicated Cardiovascular Serious Adverse Events Through Month 12 and Overall Study Periods (DCRI Adjudication of Study 337, Study 142, and Studies 337 and 142 Meta-analysis)



HR = hazard ratio; Meta = meta-analysis; Romo = romosozumab

Source: Figures 14z-6.5.9. and 14z-6.5.10

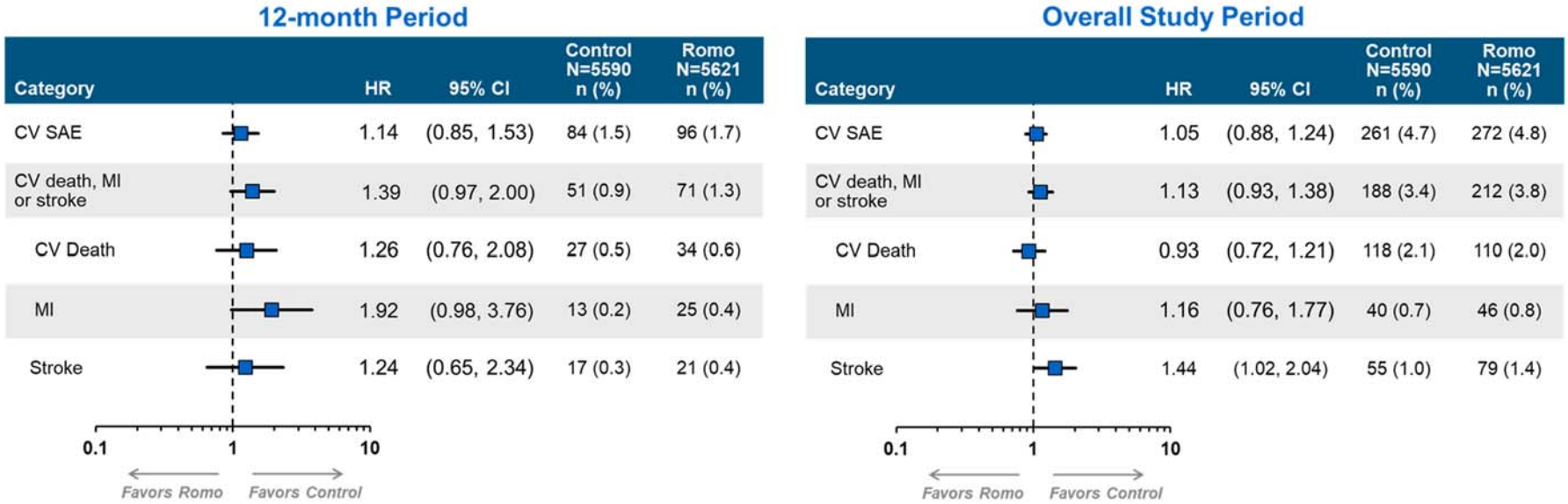
Figure 24. Time to First MACE Through Month 12 and the Overall Study Period (DCRI Adjudication of Study 337, Study 142, and Studies 337 and 142 Meta-analysis)



HR = hazard ratio; Meta = meta-analysis; Romo = romosozumab

Source: Figures 14z-6.5.11. and 14z-6.5.12

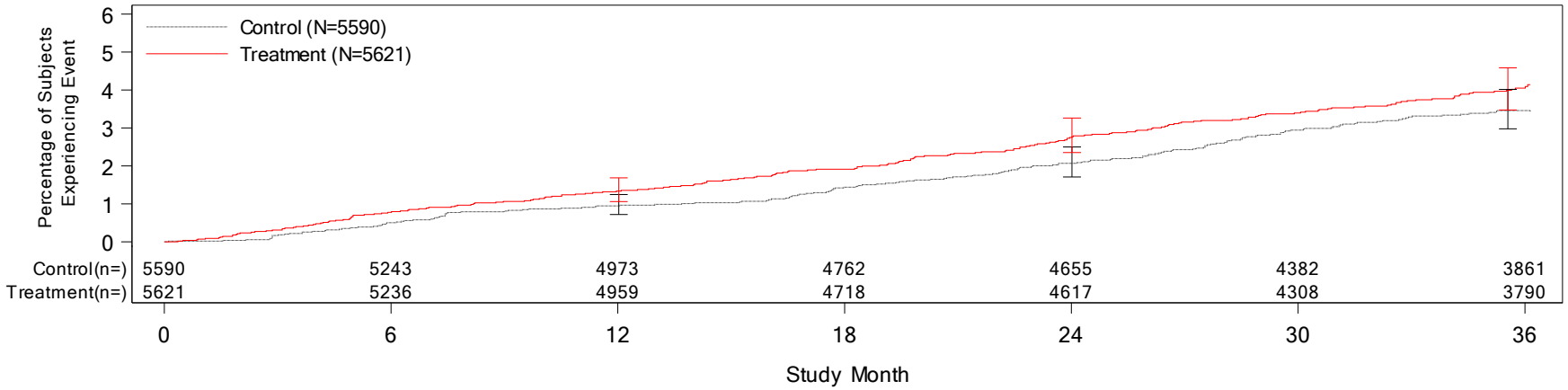
Figure 25. Meta-analysis: Time to First Occurrence of Positively-Adjudicated CV SAEs, MACE Composite and Components in the 12-Month Double-blind and Overall Study Periods (DCRI Adjudication of Studies 337 and 142 Meta-analysis)



CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; Romo = romosozumab

Source: Figure 14z-6.7.5 and Figure 14z-6.7.10

Figure 26. Kaplan-Meier Plot of Time to First MACE (Composite of CV Death, MI and Stroke) in the Overall Study Period (Meta-analysis of Studies 337 and 142)



N = Number of subjects in the safety analysis set
n = Number of subjects at risk for event at time point of interest
'Treatment' = romosozumab/denosumab or romosozumab/alendronate; 'Control' = placebo/denosumab or alendronate/alendronate
Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Subjects received open-label denosumab after the 12-month double blinded period.
Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Subjects received open-label alendronate after the 12-month double blinded period.
The timepoint for study month 36 is set at study day 1082 (study day 1096 - 14 days).
Death events include fatal events adjudicated as cardiovascular-related or undetermined.

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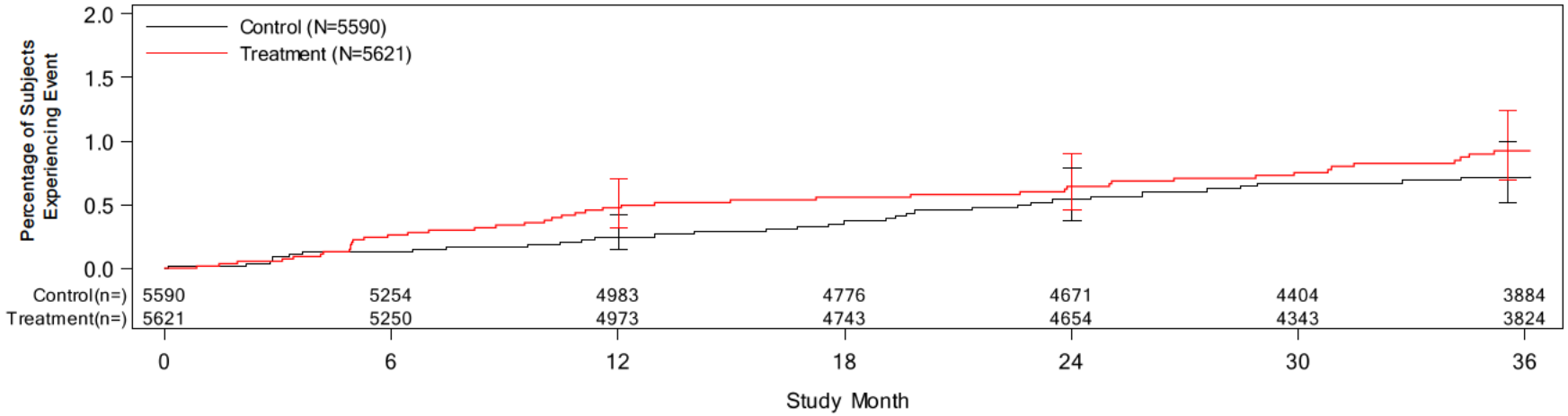
Output: f14z-06-002-014-km-mace-eos-337-142-duke.rtf (Date Generated: 28NOV18 13:17) Source Data: cviss.adsl, cviss.adttes

Source: Figure 14-6.2.1.3, CV Report

Figure 27. Kaplan-Meier Plots of Time to First Positively-Adjudicated MI Over 36 Months (Meta-analysis of Studies 337 and 142)



N = Number of subjects in the safety analysis set

n = Number of subjects at risk for event at time point of interest

'Treatment' = romosozumab/denosumab or romosozumab/alendronate; 'Control' = placebo/denosumab or alendronate/alendronate

Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Subjects received open-label denosumab after the 12-month double blinded period.

Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Subjects received open-label alendronate after the 12-month double blinded period.

The timepoint for study month 36 is set at study day 1082 (study day 1096 - 14 days).

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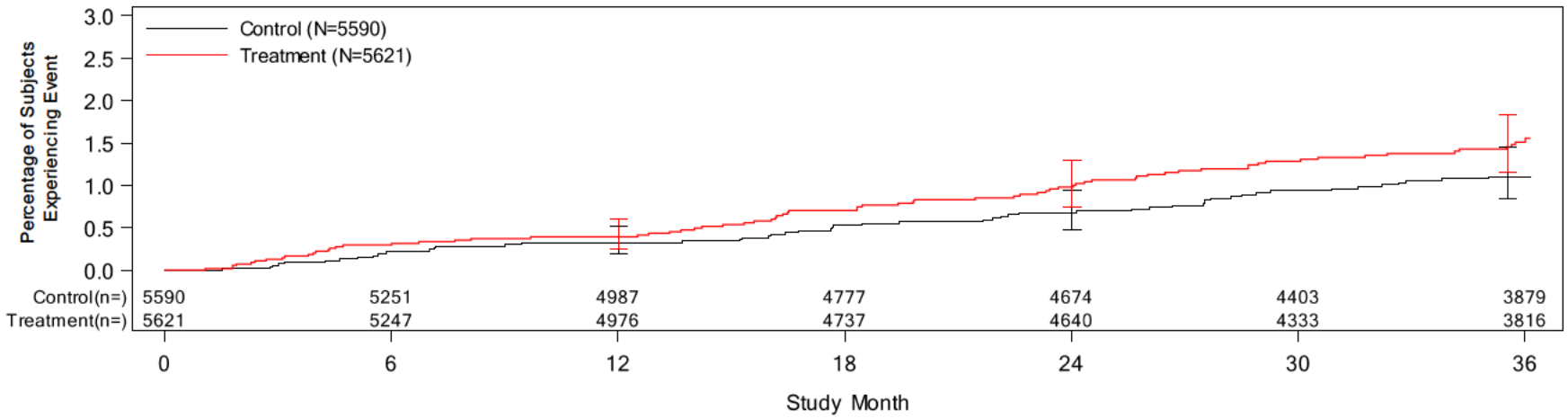
Figure 28. Kaplan-Meier Plots of Time to First Positively-Adjudicated Stroke Over 36 Months (Meta-analysis of Studies 337 and 142)



N = Number of subjects in the safety analysis set

n = Number of subjects at risk for event at time point of interest

'Treatment' = romosozumab/denosumab or romosozumab/alendronate; 'Control' = placebo/denosumab or alendronate/alendronate

Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Subjects received open-label denosumab after the 12-month double blinded period.

Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Subjects received open-label alendronate after the 12-month double blinded period.

The timepoint for study month 36 is set at study day 1082 (study day 1096 - 14 days).

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8.6 Subgroup Analyses

Various post hoc subgroups based on baseline CV risk factors were examined to see if there was a patient population that had a higher or lower risk for positively-adjudicated CV SAEs with romosozumab treatment. These analyses should be interpreted with caution as many of these subgroups have a small number of subjects with positively-adjudicated MACE events.

Studies 337 and 142 collected the following information relevant to the assessment of CV risk: age; blood pressure; general medical history which could be queried for prior MI, prior stroke, hypertension, diabetes mellitus, and hypercholesterolemia; smoking history; creatinine; and concomitant medications. Fasting lipid values, HbA1C, or high sensitivity C-reactive protein were not obtained; hence CV risk estimation via standard cardiovascular risk calculators, eg, Framingham Risk Score, American College of Cardiology (ACC)/American Heart Association (AHA) CV risk estimator, the Reynolds Score, is not possible without modification of the calculator or imputation of data.

In a meta-analysis of Studies 337 and 142, the relative risk of CV events with romosozumab compared to control was generally consistent across subgroups of CV risk factors including age, smoking history, prior history of MI and stroke, and other CV risk factors (Figure 29 for the double-blind period and Figure 30 for the overall study period). No subgroup was identified where subjects were at increased relative risk of MACE with romosozumab treatment compared with control in the high risk subgroup compared with the lower risk subgroup. There was, not surprisingly, a greater absolute risk of MACE in subjects with a prior MI or stroke. The incidence of MACE was 3.6% and 2.1% in the romosozumab and control arms, respectively, in subjects with prior history of MI or stroke vs 1.1% and 0.8% in those without a prior history at 12 months (Figure 29). In the overall study period, this increased to 8.9% and 5.8% in the subjects with prior MI or stroke in the romosozumab/antiresorptive arm and control/antiresorptive arm, respectively, compared to 3.5% and 3.2% in those without a prior MI or stroke (Figure 30). Excluding atrial fibrillation/atrial flutter, the prior MI or stroke subgroup had the higher subject incidence of MACE than CV risk factors, like diabetes mellitus or hypertension.

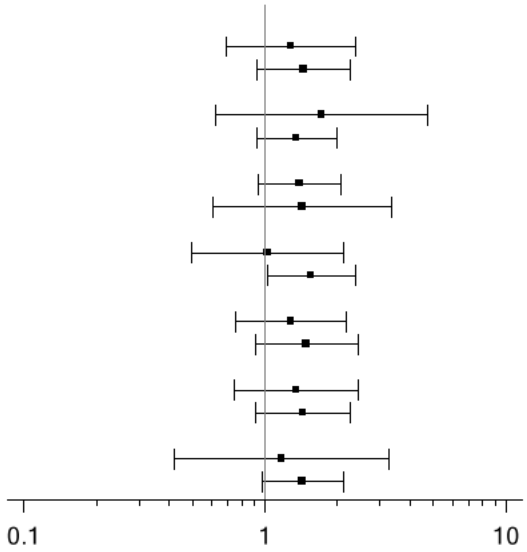
Subgroup analyses by geographic region are provided for the double-blind and overall study periods in Figure 31. The percentages of subjects in the full analysis set by region was 11% from Asia Pacific and South Africa, 33% from Central/Eastern Europe and Middle East, 40% from Central/Latin America, 3% from North America, and 13% from

Western Europe and Australia/New Zealand. When MACE events were analyzed by these regions, there was no treatment-by-subgroup interaction among regions for either period.

In summary, despite the limitations of these subgroup analyses, there does not appear to be a subpopulation at consistently increased relative risk with romosozumab compared with control.

Figure 29. Subgroup Analyses of Baseline CV Risk Factors: Time to First Occurrence of MACE Through Month 12 (Meta-analysis of Studies 337 and 142)

Category		Placebo or Alendronate N = 5590 n/N1 (%)	Romosozumab 210 mg QM N = 5621 n/N1 (%)	HR (95% CI)
Age	< 75 years	18/3426 (0.5)	23/3434 (0.7)	1.28 (0.69, 2.38)
	≥ 75 years	33/2164 (1.5)	48/2187 (2.2)	1.45 (0.93, 2.26)
Prior MI or Stroke	Yes	6/291 (2.1)	10/280 (3.6)	1.73 (0.63, 4.75)
	No	45/5299 (0.8)	61/5341 (1.1)	1.35 (0.92, 1.99)
Hypertension	Yes	42/3146 (1.3)	58/3138 (1.8)	1.39 (0.94, 2.07)
	No	9/2444 (0.4)	13/2483 (0.5)	1.43 (0.61, 3.35)
Diabetes	Yes	15/748 (2.0)	14/697 (2.0)	1.03 (0.50, 2.13)
	No	36/4842 (0.7)	57/4924 (1.2)	1.56 (1.03, 2.37)
Hypercholesterolemia	Yes	24/2083 (1.2)	31/2088 (1.5)	1.28 (0.75, 2.19)
	No	27/3507 (0.8)	40/3533 (1.1)	1.49 (0.91, 2.43)
Smoking	Current/Former	20/1628 (1.2)	25/1515 (1.7)	1.35 (0.75, 2.43)
	Never	31/3962 (0.8)	46/4105 (1.1)	1.44 (0.91, 2.27)
Afib/Aflutter	Yes	7/152 (4.6)	8/151 (5.3)	1.17 (0.42, 3.26)
	No	44/5438 (0.8)	63/5470 (1.2)	1.43 (0.98, 2.11)



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period; N1 = Number of subjects in the subgroup
Hazard ratio and 95% CI are based on the Cox proportional hazard model comparing romosozumab versus 'control' (either placebo or alendronate).

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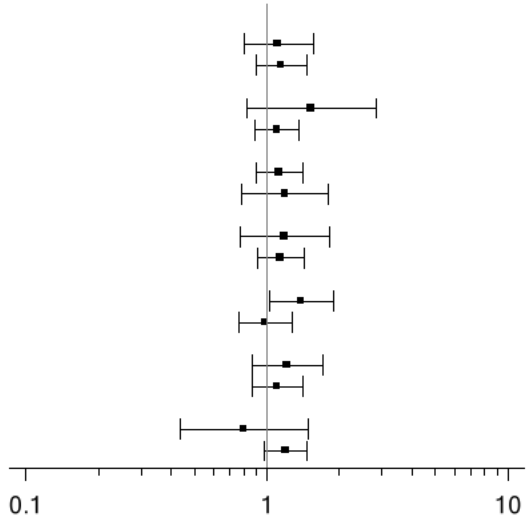
Figure 30. Subgroup Analyses of Baseline CV Risk Factors: Time to First Occurrence of MACE in the Overall Study Period (Meta-analysis of Studies 337 and 142)



Category		Control N = 5590 n/N1 (%)	Treatment N = 5621 n/N1 (%)	HR (95% CI)
Age	< 75 years	67/3426 (2.0)	74/3434 (2.2)	1.11 (0.80, 1.55)
	≥ 75 years	121/2164 (5.6)	138/2187 (6.3)	1.15 (0.90, 1.47)
Prior MI or Stroke	Yes	17/291 (5.8)	25/280 (8.9)	1.53 (0.82, 2.84)
	No	171/5299 (3.2)	187/5341 (3.5)	1.10 (0.89, 1.35)
Hypertension	Yes	146/3146 (4.6)	162/3138 (5.2)	1.12 (0.90, 1.40)
	No	42/2444 (1.7)	50/2483 (2.0)	1.19 (0.79, 1.79)
Diabetes	Yes	42/748 (5.6)	43/697 (6.2)	1.18 (0.77, 1.81)
	No	146/4842 (3.0)	169/4924 (3.4)	1.14 (0.91, 1.42)
Hypercholesterolemia	Yes	69/2083 (3.3)	96/2088 (4.6)	1.39 (1.02, 1.89)
	No	119/3507 (3.4)	116/3533 (3.3)	0.98 (0.76, 1.27)
Smoking	Current/Former	64/1628 (3.9)	72/1515 (4.8)	1.22 (0.87, 1.70)
	Never	124/3962 (3.1)	140/4105 (3.4)	1.10 (0.87, 1.41)
Afib/Aflutter	Yes	25/152 (16.4)	18/151 (11.9)	0.80 (0.44, 1.47)
	No	163/5438 (3.0)	194/5470 (3.5)	1.20 (0.97, 1.47)

N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period; N1 = Number of subjects in the subgroup
Hazard ratio and 95% CI are based on the Cox proportional hazard model comparing 'Treatment'(romosozumab/denosumab or romosozumab/alendronate) versus 'Control'(placebo/denosumab or alendronate/alendronate).

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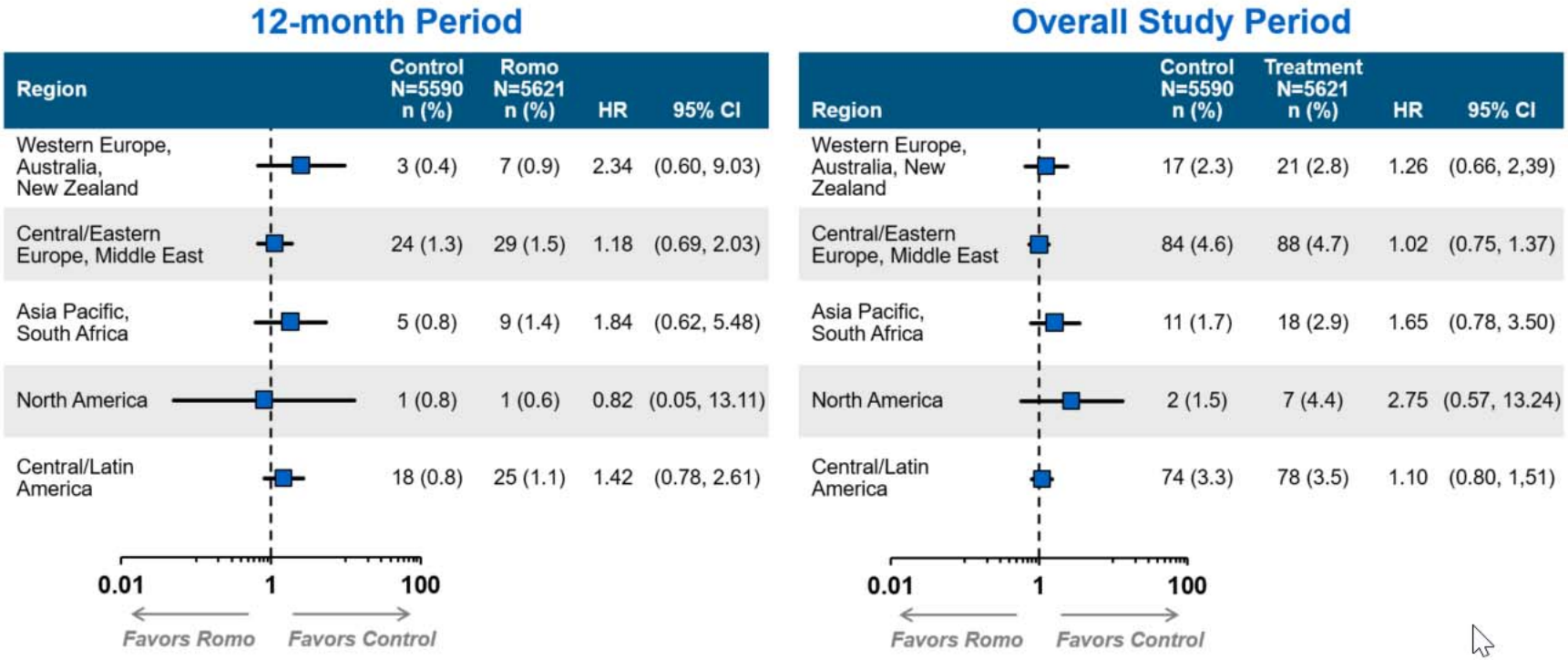
Figure 31. Subgroup Analyses by Geographic Region: Time to First Occurrence of MACE Through Month 12 and Overall Study Periods (Meta-analysis of Studies 337 and 142)



8.7 Cardiovascular Vital Signs

Neither the nonclinical safety pharmacology program nor the phase 1, 2, and 3 clinical program indicated any relevant changes in mean blood pressure and/or heart rate. Mean values were comparable between treatment groups at baseline and throughout each of the studies.

Review of the diastolic and systolic blood pressure shifts from baseline among all subjects and in subjects with positively-adjudicated cardiovascular events during the double-blind periods of Studies 337 and 142 did not suggest that romosozumab impacts blood pressure, as shifts were comparable between treatment groups within each study.

Lipids were not collected in the 3 pivotal, phase 3 studies.

8.8 Summary of Cardiovascular Safety

In the pivotal, alendronate-controlled study in postmenopausal women with osteoporosis with prior fracture (Study 142), there was a higher incidence of positively-adjudicated CV SAEs in the first year in the romosozumab group compared with the alendronate group (50 [2.5%] vs 38 [1.9%], romosozumab vs alendronate, respectively). This was driven primarily by MI and stroke. The incidence of these events in the first year was the same between romosozumab and placebo in the placebo-controlled study in postmenopausal women with osteoporosis (Study 337) (46 [1.3%] in both treatment groups). The meta-analysis of Studies 337 and 142 with 122 subjects with MACE events had a HR (95% CI) of 1.39 (0.97, 2.00).

In the overall study period for Studies 337 and 142, the incidence of positively-adjudicated CV SAEs was generally balanced except for a higher incidence of stroke events on romosozumab in Study 142. The meta-analysis of Studies 337 and 142 with 400 subjects with MACE events had a HR (95% CI) of 1.13 (0.93, 1.38).

Extensive nonclinical evaluations did not identify a pathobiological mechanism.

Subgroup analyses did not identify a population at consistently increased relative risk of MACE with administration of romosozumab. However, as expected, subjects with a history of MI or stroke had a higher absolute increase in risk.

Despite its limitation, the meta-analysis represents the best estimate of the risk of MACE for the determination of benefit: risk. There is a possible increased risk of MI and stroke with romosozumab that has been well-characterized based on a total of 122 subjects with positively-adjudicated MACE events yielding a hazard ratio for MACE of 1.39 with

the upper bound 95% CI of 2.00 in the 12-month double-blind period from a meta-analysis of Studies 337 and 142. For the overall study period, which characterizes the risk associated with the treatment strategy of romosozumab followed by antiresorptive therapy, the hazard ratio for MACE is 1.13 with the upper bound 95% CI of 1.38 based on a robust 400 positively-adjudicated MACE events.

9. Pharmacovigilance and Risk Management

9.1 Routine Pharmacovigilance and Risk Management Measures

To address the possible risk of MI and stroke, communication of risks for romosozumab in the proposed product labeling, including a boxed warning for events of MI and stroke, is proposed. A patient medication guide will also describe safety risks of CV events of MI and stroke, ONJ, and AFF. In addition, patient and healthcare provider educational material and a support call center for questions will be available to further encourage informed benefit-risk decisions.

The safety of romosozumab will be monitored with a comprehensive pharmacovigilance plan, including a robust program to monitor the safety of romosozumab in the postmarketing setting. Review and implementation of pharmacovigilance activities will be based on ongoing signal detection including collection, confirmation, and analysis of adverse drug reactions, systematic identification of various failure modes for the prefilled syringe, product/device incident and malfunction reports, medical/scientific literature review, external patient database reviews, and adjudication in clinical studies, as appropriate, for all potential cases of CV SAEs, ONJ, and AFF. Detailed questionnaires for MI and stroke will be included in adverse event reporting as part of this pharmacovigilance plan.

Any newly-identified safety signals detected through pharmacovigilance activities will be further evaluated and, if deemed necessary, appropriate actions will be taken. Periodic safety reports will be provided to FDA per regulatory requirements.

Amgen is committed to working with FDA on appropriate post-marketing commitments to better characterize the CV safety findings.

9.2 Proposed Noninterventional Study

The meta-analysis of the data from Studies 337 and 142 suggest that there is a possible risk of MI and stroke with romosozumab; based on these data, the magnitude of this possible risk is not likely to exceed a 2-fold increase (12-month period MACE HR = 1.39 [95% CI: 0.97, 2.00]). To further characterize this possible risk, specifically to determine that the risk of MACE in patients receiving romosozumab does not exceed a 2-fold increase relative to comparator, Amgen considered two options: 1) a pre- or post-approval, randomized, double-blind, non-inferiority trial, or 2) a non-interventional study. Based on the rationale provided below, it is the opinion of the Sponsor that this possible risk can be best characterized in the proposed post-marketing non-interventional study.

While postmenopausal women in Studies 337 and 142 were on average 71 to 74 years of age with CV risk factors (eg, hypertension, hypercholesterolemia, smoking, diabetes), the percentage of patients at high CV risk defined as a prior history of MI or stroke was approximately 5%. The incidence of MACE in the romosozumab study population was ~1.0% annually. This incidence is low compared to the general patient population with prior MI or stroke, in whom the incidence of MACE is ~3.0% annually. The number of subjects with MACE in the clinical trial program was 122 at 12 months and 400 in the overall study period. The HR and 95% CIs were 1.39 (95% CI: 0.97, 2.00) and 1.13 (95% CI: 0.93, 1.38) for the 12-month and overall study periods, respectively. The number of events observed in two trials and the meta-analysis described in Section 8.5.3.2 suggest that the possible CV risk of romosozumab is unlikely to exceed a 2-fold increased risk of MACE. The characterization of the possible CV risk to date, the low prevalence of prior MI or stoke in the intended population, and the relatively low incidence of MACE in this population suggest that further data generation can be performed in the post-marketing setting.

A post-marketing, non-interventional study provides an opportunity to evaluate this possible risk in a large number of US patients eligible to receive or receiving romosozumab. The proposed non-interventional post-marketing study will determine the incidence rates of MACE, MI, stroke, and death due to any cause in women with postmenopausal osteoporosis (PMO) receiving romosozumab compared with risk matched women with PMO exposed to standard of care osteoporosis pharmacotherapy. Demographic and clinical characteristics of patients exposed to romosozumab and other osteoporosis therapies will also be described. The study will utilize large administrative claims healthcare databases, including the US Medicare database, allowing the evaluation of a large number of US women exposed to romosozumab. Based on our prior experience, the Medicare database is expected to contribute close to half a million unique patients with PMO per year, and this population will be supplemented with information from other databases. The proposed study databases provide rapid data access, with a data lag of approximately 3 to 6 months. This will enable interim evaluations at appropriate intervals prior to reporting final study results. Cardiovascular outcomes such as MI and stroke are well documented in healthcare databases, and algorithms for identifying these events in these databases have been shown to have high validity when compared against medical records (Kumamaru et al, 2014; Kiyota et al, 2004; Birman-Deych et al 2005; Wahl et al 2010). Analytic methods including propensity score methods, inverse probability of treatment weights (IPTW),

inverse probability of censoring weights (IPCW) and quantitative bias assessment will be used to mitigate against and assess the potential impact of confounding. These case ascertainment algorithms and statistical approaches have been used successfully in previous CV studies within administrative healthcare databases, including our proposed databases (Fralick et al, 2018; Weintraub et al, 2012). For example, a recent cohort study conducted within the Truven MarketScan administrative claims database compared risk of CV outcomes between patients using telmisartan vs those using ramipril (Fralick et al, 2018). This study yielded results similar to those of the ONTARGET randomized trial. The risk ratios for the study endpoints of MI, stroke, congestive heart failure, angioedema, as well as a composite study endpoint of MI, stroke or hospitalization for congestive heart failure, were similar between the non-interventional database study and the randomized controlled trial (Fralick et al, 2018). The CV clinical outcomes evaluated in this study, which are well captured in administrative databases, along with the investigators' use of appropriate study design and statistical methods, enabled the validity of the study findings.

Results from a post-marketing non-interventional study will be available in a timely manner. The proposed non-interventional study will begin within one year of BLA approval, and we anticipate that approximately 8000 romosozumab users with PMO will accrue in the planned databases during the first 2 years of the study. Applying an annual event rate of MACE of 1.5% (ie, a slightly higher incidence in clinical practice vs that observed in clinical trials), 244 patients are expected to have experienced MACE in the study within the first 2 years, including romosozumab-treated patients and romosozumab-eligible matched controls. A total of 88 events are required to exclude excess risk of 2.0 (upper bound of the 95% confidence interval); this number of events is projected to accrue in just over 1 year of the study. By contrast, assuming that a randomized trial (1:1) would begin at a similar timeframe following BLA approval, and applying a standard subject enrollment rate and the same event rate for MACE as in the non-interventional study, it is anticipated that 34 patients will experience MACE during the first 2 years of the study period, and that accrual of 88 patients experiencing MACE would require a study period of 3 years. A higher CV risk population could be evaluated in a randomized CV outcomes trial; however, enrichment strategies to enroll a higher CV risk population will lead to enrollment of subjects who are not representative of or represent a small minority of women with PMO eligible to receive or receiving romosozumab in clincal practice. Thus, the assumptions for the non-interventional study

provide much faster and more applicable evaluation of the possible risk of MACE with romosozumab than a randomized double-blind non-inferiority trial.

In summary, the proposed non-interventional study design and analytic methods are feasible and adequate to meet the objective of determining that the risk of MI and stroke in patients receiving romosozumab does not exceed a MACE HR of 2.0. While a non-interventional study using these databases will not have the rigor of data collection and randomization that would be present in a randomized double-blind non-inferiority trial, the use of validated algorithms to identify postmenopausal women, exposure to romosozumab and other osteoporosis therapies, and the CV events of interest, with the ability to leverage statistical methods that assess and minimize confounding, will allow the study objectives to be met. The non-interventional study provides the opportunity to evaluate our study objectives in a large number of US patients receiving romosozumab in clinical practice and obtain data in a timely manner. Amgen's prior experience evaluating safety outcomes in women with PMO in the proposed databases can also be applied to this study. Additional information about the non-interventional study design is provided below.

9.2.1 Study Objectives

The proposed overall study objectives are listed below. A detailed protocol and analytic plan will be finalized in partnership with the Agency.

1. Describe demographic and clinical characteristics, including age, risk factors for osteoporosis or cardiovascular disease, medication use, fracture events, and CV events, in women with PMO exposed to romosozumab and women with PMO exposed to standard of care osteoporosis pharmacotherapy (eg, oral and injectable bisphosphonates, denosumab, teriparatide, abaloparatide).
2. Determine incidence rates of the following outcomes among women with PMO exposed to romosozumab and women with PMO exposed to standard of care osteoporosis pharmacotherapy:
    a. MACE
    b. MI
    c. Stroke
    d. Death due to any cause
3. Compare, after adjusting for differences in confounding factors, the incidence of outcomes listed in (2) above among women with PMO exposed to romosozumab relative to that in women with PMO exposed to standard of care osteoporosis pharmacotherapy
4. Describe utilization patterns among women with PMO exposed to romosozumab

9.2.2 Study Design, Data Source, and Methods

This will be a prospective cohort study conducted using the US Medicare administrative claims database and 2 commercial administrative claims databases: Truven MarketScan and Optum. The Medicare dataset will consist of a 100% sample of female Medicare beneficiaries age ≥ 65 years with osteoporosis who are enrolled in fee-for-service Medicare Parts A, B, and D plans. Given that Medicare provides health insurance coverage for more than 90% of the elderly US population, it represents a large majority of the female population at risk of osteoporosis-related fractures who may be eligible to receive romosozumab in the US. As such, it is anticipated that the vast majority of subjects evaluated in this study will be from the Medicare database. Amgen has used this Medicare dataset in our on-going FDA postmarketing commitment study for denosumab. In that study, a total of 5 149 874 women with PMO were evaluated within the Medicare dataset during a 5-year period.

The Optum database consists of administrative claims from patients in United HealthCare, the largest single health insurance carrier in the US. The Truven MarketScan databases include information from a variety of fee-for-service and managed care plans in the US. These data systems will provide information on patients who are covered by commercial health plans, including patients younger than age 65 who are not captured through Medicare. In addition, they will also include data on patients age ≥ 65 years receiving coverage through Medicare Advantage plans (Optum) or Medicare supplemental plans (Truven Marketscan), who are not captured within the traditional fee-for-service Medicare data system described above.

9.2.3 Ascertainment of Patient Population, Exposures, and Outcomes

For Amgen's FDA post-marketing commitment study for denosumab that evaluates a variety of safety outcomes within the Medicare and Optum data systems, we have developed algorithms to identify and characterize PMO patients, and their treatments and outcomes within the administrative claims databases, which have been validated using medical charts. These algorithms will be used to identify PMO patients, and their exposure to osteoporosis treatments within the databases for the proposed non-interventional study. Romosozumab use will be identified in the databases using National Drug Codes (NDC) and drug-specific Healthcare Common Procedure Coding System (HCPCS) codes. To identify romosozumab use in the databases during the early postmarketing period prior to the availability of its drug-specific HCPCS code, we will develop algorithms based on non-specific administration codes in combination with

information such as a diagnosis of osteoporosis, NDC code, dosing interval, drug cost, etc. A similar approach was taken in the denosumab post-marketing FDA commitment study, and its validity has been demonstrated in Medicare (Curtis et al, 2013) and other administrative claims databases including Optum (Hoffman V et al, 2014).

Cardiovascular events are well documented in administrative claims databases. These events will be identified using validated algorithms based on relevant hospital discharge diagnosis codes (Kim et al, 2017). These ascertainment algorithms have been shown to have high validity when compared against medical records, with positive predictive values of approximately 90% to 95% and specificity exceeding 99% (Kumamaru et al, 2014; Kiyota et al, 2004; Birman-Deych et al 2005; Wahl et al 2010). Positive predictive value is a relevant metric of accuracy when assessing use of claims data to determine the likelihood that an individual has experienced a clinical outcome identified in the data. The high specificity of the case ascertainment algorithms is also critical, as high specificity of outcome assessment allows for nearly unbiased relative risk estimation despite imperfect sensitivity in pharmacoepidemiology studies (Schneeweiss S, Avorn J, 2005). The high positive predictive value and specificity of case ascertainment algorithms for the outcomes in this study support their valid use for purposes of comparing risk between study groups.

Information on death is available within the Medicare and Optum data systems and a subset of the Truven Marketscan database. Information specific to CV death is available directly within the Medicare data system. For the Optum database, information specific to CV death is available through linkage to the Social Security Administration death master file as well as specific claims statuses. The availability of validated algorithms with high positive predictive value support the feasibility of identifying CV events of interest in the databases.

Covariates including concomitant clinical diagnoses, medications, and osteoporosis and CV disease risk factors will be ascertained based on International Classification of Diseases (ICD) disease and procedure codes. In a cohort of PMO patients at high risk for fracture from the Medicare database (N = 1 442 551), the mean (SD) age is 79.90 (7.91) years, 86.27% of the cohort is white, 4.47% of the cohort is black, and 4.11% is Asian. Approximately 8.63% and 6.86% of patients had a history of vertebral and hip fracture, respectively. Prevalence of hypertension is 82.19%, diabetes is 27.65%, and hyperlipidemia is 27.94%. An MI had occurred in 1.49% and a stroke had occurred in 1.67% of patients in the cohort (Table 16). These data provide information supporting

the feasibility of collecting these covariates in the proposed non-interventional study. To enhance the completeness of information on cardiovascular risk factors and clinical characteristics not captured in our databases, we will explore linking the databases to additional clinical data sets. In previous studies administrative claims databases, including Medicare and commercial claims databases, have been linked to a variety of data sources including registries (Weintraub et al, 2012; Curtis et al, 2014; Nowell et al, 2018), data from laboratory providers (Curtis et al, 2018), prospective cohort studies (Xie et al, 2016), and clinical records.

9.2.4 Statistical Analyses

Summaries of the data will describe characteristics of, and incidence of outcomes among women with PMO exposed to romosozumab and women with PMO receiving standard of care osteoporosis pharmacotherapy. To assess excess risk of the outcomes of interest, incidence of those outcomes will be compared between women with PMO exposed to romosozumab and an appropriate standard of care cohort once a sufficient number of events have been accrued. When undertaking the comparative analyses, it will be important that factors associated with likelihood of receiving romosozumab versus standard of care, eg, age, duration and severity of PMO, baseline prevalence and history of CV risk factors, other comorbid conditions, and concurrent and past medications, be balanced between the romosozumab and standard of care cohorts. To mitigate against and assess the potential impact of confounders measurable in our datasets, analytic methods including propensity score methods, IPTW, and IPCW, will be employed. Use of methods such as high-dimensional propensity scores and quantitative bias analysis, will be used as appropriate to address impacts of potential confounders not measured in our data. Quantitative bias assessment is an overarching term applied to methods that estimate quantitatively the direction, magnitude, and uncertainty associated with systematic errors that influence measures of association. For example, this type of analysis can provide information on the magnitude of difference that would need to exist in the prevalence of an unmeasured confounder between study groups, in order to account for an observed difference in outcomes in an adjusted analysis. These methods have been used in previous non-interventional studies (Weintraub et al, 2012; Cadarette et al, 2008).

In summary, our methods are adequate for the purposes of meeting our objective of determining that the risk of MACE in patients receiving romosozumab does not exceed a HR of 2.0. Previous, well-designed non-interventional databases studies have

successfully achieved similar objectives when evaluating adverse events of pharmacotherapies. For example, in a study using the Medicare database Curtis et al compared risk of hospitalized infections between rheumatoid arthritis patients concurrently exposed to biologic agents and denosumab versus those concurrently exposed to biologic agents and zoledronic acid (Curtis et al, 2015). Testing a hypothesis of non-inferiority to exclude risk of 1.5 (upper limit of 95% CI) and employing propensity score methods to create risk-matched cohorts, the study concluded that risk of serious infection in the denosumab group was noninferior to that in the zoledronic acid group. Other studies in Medicare and Truven MarketScan databases, which have assessed cardiovascular outcomes, have reported results comparable to those seen in randomized controlled trial (Fralick et al, 2018; Weintraub et al 2012).

9.2.5 Study Size Considerations

Based on the null hypothesis that incidence of MACE is not higher in romosozumab-treated patients than in an appropriately matched cohort of standard-of-care-treated patients, the comparative analyses specified in objective 3 are designed to test a hypothesis of noninferiority with romosozumab treatment compared to standard of care. Assuming a 12-month follow-up period, and equal allocation to romosozumab and standard of care, a total of 88 patients with MACE events are required to demonstrate noninferiority using a margin of 2.0. Demonstrating noninferiority using lower margins of 1.8, 1.6 or 1.5 will require 122, 191, and 256 patients with MACE events, respectively.

In order to support the feasibility of the proposed study, Table 16 shows clinical characteristics and incidence of the CV events of interest observed in a cohort of fee-for-service Medicare beneficiaries with PMO who are at high risk for fracture.

Table 16. Clinical Characteristics and 1-Year Cumulative Incidence of Myocardial Infarction, Stroke, and Death Among Women With PMO at High Risk for Fracture Within the Fee-for-Service Medicare Database

Patient Characteristics	Women with PMO and High Risk for Fracture N = 1 442 551
Mean age (SD)	79.90 (7.91)
Baseline[a] prevalence of hypertension	82.19%
Baseline[a] prevalence of hyperlipidemia	27.94%
Baseline[a] prevalence of diabetes	27.65%
Baseline[a] prevalence of stroke	1.67%
Baseline[a] prevalence of MI	1.49%
1-year cumulative incidence of stroke (95% CI)	1.12% (1.11, 1.14)
1-year cumulative incidence of MI (95% CI)	1.38% (1.36, 1.40)
1-year cumulative incidence of death (95% CI)	8.69% (8.64, 8.74)

MI = myocardial infarction; PMO = postmenopausal osteoporosis
[a] Baseline prevalence is based on presence of relevant diagnosis codes over a 24-month look-back period in the database

Based on the incidence of MACE events and the prevalence of MI and stroke observed in the population of women with PMO at high risk for fracture from the Medicare data system (Table 16), the expected incidence of MACE in the population of PMO women who will use romosozumab in routine clinical practice is approximately 1.5%. Since the Medicare dataset is the largest, we have used this dataset to determine projected accrual of romosozumab patients. In our ongoing postmarketing FDA commitment study for denosumab, 34 004 eligible women with PMO using denosumab were accrued during the first year following market authorization in the fee-for-service Medicare database. An additional 40 212, 49 194, 65 698, and 66 036 women with PMO using denosumab were accrued during the second, third, fourth, and fifth years following market authorization, respectively. For the proposed romosozumab study, we have applied an assumption that romosozumab users in routine clinical practice will represent a higher risk sub-population of PMO patients compared to women with PMO who use denosumab. Consequently, we have assumed that the size of the romosozumab patient population will be approximately 15% of the size of the denosumab PMO population observed in the denosumab study. Table 17 provides an estimate of the accrual of MACE by year of the proposed study, taking into account the event rate, anticipated romosozumab patient exposure, and anticipated data lag of up to 6 months in the database.

Table 17. Anticipated Timing of Accrual of Study Participants and MACE Events

Study Year	Incremental Number of Romosozumab Users With PMO in Medicare Study Database	Cumulative Number of Romosozumab Users With PMO Observable[a] in Medicare Study Database	Cumulative Number of MACE Events Observed Across Romosozumab and SOC Comparator Patients[b]	Magnitude Of Excess Risk Excluded (Hazard Ratio)
1	5100	2550	76	--
2	11132	8116	244	1.6
3	18512	14822	444	1.5

MACE = major adverse cardiovascular event; PMO = postmenopausal osteoporosis; SOC = standard of care

[a] Takes into consideration anticipated data lag and limitations related to identifying romosozumab within database in early post-marketing period prior to availability of drug-specific Healthcare Common Procedure Coding System (HCPCS) code

[b] Assumes annual MACE event rate of 1.5%

Milestones

Study findings will be summarized in annual reports included in the Periodic Benefit Risk Evaluation Reports (PBRER) to the regulatory agency. A final report will be completed following the end of the study.

10. Benefits and Risks Conclusions

Postmenopausal osteoporosis is a chronic progressive disease that increases the risk of fractures. After an osteoporosis-related fracture, the risk of a subsequent fracture is 5-fold higher in the first year and remains elevated for 10 years. Even if recovery after the first fracture allows a woman to remain pain-free and independent, subsequent fractures will ultimately lead to chronic pain, loss of independence and earlier death, compared to postmenopausal women who have not suffered fractures. There is a clear unmet need in women with osteoporosis at high risk for fracture, particularly those with a recent fracture, to strengthen bone and rapidly reduce fracture risk across the skeleton. It is anticipated that healthcare professionals will use romosozumab in this vulnerable patient population.

Through its dual mechanism of action, romosozumab rapidly increases BMD at the lumbar spine and hip, starting as early as 6 months; these gains were superior to both alendronate and teriparatide through 12 months of therapy and continued to accrue when transitioned to antiresorptive therapy. Romosozumab rapidly reduced fractures within 12 months. Long-term anti-fracture efficacy also continued after transition to antiresorptive therapy. This is the first large osteoporosis program to show anti-fracture efficacy across a range of anatomical sites (vertebral, clinical, and nonvertebral, including hip, fractures) compared with alendronate, the most commonly used antiresorptive therapy. In summary, romosozumab can benefit patients at high risk for fracture who need a more potent bone-forming agent to rapidly reduce fracture risk.

Romosozumab's safety profile was evaluated in more than 14 000 subjects. Key safety risks from a non-cardiovascular standpoint include hypersensitivity reactions, hypocalcemia, and rare cases of ONJ and AFF. These risks are consistent with those of other osteoporosis products and all are manageable. There was a higher incidence of positively-adjudicated CV SAEs in the alendronate-controlled Study 142, which was driven by a higher incidence of MI and stroke. The incidence of positively adjudicated CV SAEs was identical between the romosozumab and placebo arms in the placebo-controlled Study 337. Given the modest number of CV SAEs in individual trials in the 12-month double-blind period, a meta-analysis was performed which showed a HR for time to first MACE of 1.39 (95% CI: 0.97, 2.00) at 12 months based on 122 MACE events and 1.13 (95% CI: 0.93, 1.38) for the entire study based on 400 MACE events.

Given the totality of the data, the benefit of marked fracture risk reduction in postmenopausal women at high fracture risk is weighed against the possible increased risk of MI and stroke that is estimated at a MACE HR of 1.39 with an upper-bound 95% CI of 2.00 at month 12 and 1.13 with an upper-bound 95% CI of 1.38 for the overall study period. Labeling, including a boxed warning, is proposed to communicate this potential risk. In addition, a robust non-interventional post-marketing cohort study is planned to exclude a 2-fold risk of MACE in postmenopausal women at high fracture risk receiving romosozumab compared with other osteoporosis therapies. It is anticipated that data from this study will be available within 3 years post-approval. Evaluation of this possible risk in the intended US patient population and the timely data availability afford advantages over other trial options to further investigate the relationship between romosozumab and CV events. In conclusion, the benefit-risk of romosozumab in postmenopausal women at high risk for fracture is favorable, provided that the important possible risk of MI and stroke is effectively communicated in the USPI and further investigated post-marketing.

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12. Appendices

Appendix 1. Phase 2 and 3 Efficacy and Safety Studies

Study	Phase	Study Population/ Number of Subjects Enrolled	Key Study Features	Treatment Regimen	Primary Objectives	Primary Efficacy Results
337	3	Women with PMO N = 7180	Pivotal fracture study of romosozumab vs placebo	**Up to month 12**: Blinded placebo or romosozumab 210 mg SC QM **Months 12-36**: Open-label denosumab 60 mg SC Q6M	Assess effect on incidence of new vertebral fracture with: • romosozumab vs placebo through 12 months and • romosozumab for 12 months followed by denosumab for 12 months vs placebo for 12 months followed by denosumab for 12 months	• RRR of 73% on new vertebral fracture through 12 months with romosozumab vs placebo (ARR = 1.30% [0.79, 1.80]), • RRR of 75% on new vertebral fracture through month 24 after transitioning to denosumab (ARR = 1.89% [1.30, 2.49])
142	3	Women with PMO at high risk for fracture N = 4093	Pivotal fracture study of romosozumab vs alendronate	**Up to month 12**: double-dummy alendronate 70 mg PO QW or romosozumab 210 mg SC QM **Month 12 to end of study:** open-label alendronate 70 mg PO QW	Assess effect of romosozumab for 12 months followed by alendronate treatment compared with alendronate alone on incidence of new vertebral fracture through month 24 and clinical fracture at primary analysis	• RRR of 50% for new vertebral fracture through 24 months with romosozumab/alendronate vs alendronate alone (ARR = 4.03% [2.50, 5.57]) • RRR of 27% for clinical fracture after median of 33 months (ARR = 3.4% [1.40, 5.30]) for romosozumab/alendronate vs alendronate alone
289	3b	Women with PMO previously treated with bisphosphonate therapy at high risk of fracture N = 436	Open-label study of romosozumab vs teriparatide	**12 months:** Open-label teriparatide 20 µg SC QD or romosozumab 210 mg SC QM	Assess effect of romosozumab for 12 months vs teriparatide for 12 months on total hip BMD	Larger gains in total hip BMD with romosozumab vs teriparatide through month 12 (mean difference from baseline 3.2% (95% CI: 2.7%, 3.8%)

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See last page of table for footnotes and abbreviations.

Study	Phase	Study Population/ Number of Subjects Enrolled	Key Study Features	Treatment Regimen	Primary Objectives	Primary Efficacy Results
174	3	Men with osteoporosis N = 245	Placebo-controlled study in men randomized 2:1 to romosozumab or placebo	**12 months:** Blinded placebo or romosozumab 210 mg SC QM (1:2 randomization)	Assess effect of romosozumab vs placebo for 12 months on lumbar spine BMD	Not applicable (only CV safety data are included from this study)
326	2a	Postmenopausal women with low BMD N = 419	Dose-ranging, placebo- and active-controlled, study with 24-month treatment, off-treatment, and retreatment periods	**Up to month 24:** Placebo or romosozumab 70, 140, or 210 mg SC QM or 140 or 210 mg SC Q3M, or teriparatide 20 µg SC QD (12 months), or alendronate 70 mg PO QW (12 months) followed by romosozumab 140 mg SC QM (12 months) **Months 24-36:** Placebo or denosumab 60 mg SC Q6M **Months 36-48:** Romosozumab 210 mg SC QM **Months 48-72:** Zoledronic acid 5 mg IV or no intervention	Assess effect of romosozumab vs placebo for 12 months on lumbar spine BMD	Significant increases in lumbar spine, total hip, and femoral neck BMD at 12 months with all romosozumab groups vs placebo.
156	3	Women with PMO N = 294	Noninferiority study of romosozumab 90 mg/mL concentration vs 70 mg/mL concentration	**6 months:** Blinded placebo or romosozumab 210 mg SC QM (90 mg/mL or 70 mg/mL)	Assess noninferiority of treatment with romosozumab 90 mg/mL vs 70 mg/mL concentration for 6 months on BMD at lumbar spine	Romosozumab 90 mg/mL was noninferior to 70 mg/mL as measured by percent change from baseline in lumbar spine BMD
291	2b	Japanese women with PMO N = 252	Dose-ranging study of multiple doses of romosozumab vs placebo	**12 months:** Placebo or romosozumab 70, 140, or 210 mg SC QM	Assess effect of romosozumab for 12 months vs placebo for 12 months on lumbar spine BMD	Dose-dependent increases in BMD at the lumbar spine, total hip, and femoral neck vs placebo (largest gains with romosozumab 210 mg).

ARR = absolute risk reduction; BMD = bone mineral density; IV = intravenous; PMO = postmenopausal osteoporosis; Q3M = every 3 months; Q6M = every 6 months; QD = daily; QM = once monthly; QW = weekly; RANKL = Receptor activator of nuclear factor kappa-B ligand; RRR = relative risk reduction
Source: Individual CSRs

Appendix 2. Statistical Methods

Table 18. Summary of Analysis Methods for Fracture, BMD, and Bone Turnover Marker Endpoints in the Pivotal Fracture Studies (337 and 142)

Endpoints	Methods
Binary fracture endpoints Subject incidence of: • new vertebral fracture • new or worsening vertebral fracture • multiple new or worsening vertebral fracture	• Based on primary analysis set for vertebral fractures • Summarized by randomized treatment group as the number and percentage of subjects having the designated fracture type • Compared using a logistic regression model with treatment as the main effect and covariates specific to each pivotal fracture study (age and prevalent vertebral fracture strata in Study 337 and age stratum, presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score in Study 142); odds ratio, 95% CI, and p-value (score test) were provided • Also evaluated using Mantel-Haenszel method adjusting for covariates noted above to generate point estimates of absolute risk reduction (difference in proportions, control – treatment), risk ratio (ratio of proportions, treatment over control), and 95% CIs
Time to event fracture endpoints Subject incidence of: • nonvertebral fracture • clinical fracture • major nonvertebral fracture • major osteoporotic fracture • clinical vertebral fracture • hip fracture • all osteoporotic fracture (Study 142 only)	• Based on full analysis set • Summarized descriptively by randomized treatment group as the number and percentage of subjects having the designated fracture type and using Kaplan-Meier estimates at time point(s) of interest (ie, month 12, month 24, or primary analysis) • Compared using a stratified Cox proportional hazards model controlling for age and prevalent vertebral fracture strata (Study 337) or age stratum, presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score (Study 142), with treatment as the independent variable; estimated hazard ratio, 95% CI, and p-value (score test) were provided • Also evaluated using inverse variance-weighted method to produce point estimate of the adjusted risk difference (difference in Kaplan-Meier estimates at the time point of interest, control arm - treatment arm) and 95% CI • Subjects with no event of interest were censored for analysis of that event at the end of double-blind period (month 12 analysis), at the end of the 24-month study period (month 24 analysis), or at the end of the primary analysis period (Study 142 only)

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Table 18. Summary of Analysis Methods for Fracture, BMD, and Bone Turnover Marker Endpoints in the Pivotal Fracture Studies (337 and 142)

Endpoints	Methods
Time to event fracture endpoints (continued)	• In Study 142, the nonvertebral fracture endpoint was tested using a group sequential approach at the primary analysis based on a 1-sided test ($\alpha = 0.025$). The Lan-DeMets alpha spending function that approximates a Pocock boundary was used to determine the significance level at the time of the primary analysis. The significance level was calculated based on the information fraction in the alpha spending function (number of nonvertebral fracture events at primary analysis relative to the 440 planned nonvertebral fracture events for the final analysis).
DXA BMD endpoints	• ANCOVA model with treatment, age, prevalent vertebral fracture strata (Study 337), presence or absence of severe vertebral fracture at baseline (Study 142), and baseline value of the endpoint. • Additional covariates of machine type and machine type-by-baseline value interaction were included in the model for parameters derived by DXA. • Treatment comparison at each time point of interest was based on LS mean of the treatment difference (treatment - control) and 95% CI. • Results were also displayed graphically for a visual summary. • Sensitivity analyses included a repeated measures mixed effects model.
Bone Turnover Marker	• Bone turnover markers and biomarkers analyzed using non-parametric methodology • Rank tests used to compare between treatment groups
QCT BMD endpoints	• Percent change from baseline in the failure load and the other HR-pQCT parameters were analyzed by ANCOVA.

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ANCOVA = analysis of covariance; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; HR-pQCT = high resolution peripheral QCT; LS = least squares; PA = primary analysis; QCT = quantitative computed tomography

Source: Section.8.8.5 of Study 337 and Section 8.8.6 of Study 142 PA

Appendix 3. Statistical Testing Sequence in Studies 337 and 142

In Studies 337 and 142, the statistical significance for the primary and selected key secondary endpoints were controlled for multiplicity using sequential testing procedure outlined in Figure 32 for Study 337 and Figure 33 for Study 142 and to maintain the overall significance level for the study at 0.05. With this procedure, the formal inferential testing was performed for a step only when statistical significance was declared for all endpoints tested in the previous steps. If the testing sequence stopped at a particular step, the remaining endpoints in the testing sequence were not formally tested for statistical significance and the corresponding p-values were considered descriptive. The p-values for the analyses of other secondary, exploratory, and substudy endpoints were nominal without adjusting for multiplicity. All p-values were 2-sided.

In Study 142, if both the primary endpoints were significant at the 0.05 level (2-sided), each of the secondary BMD endpoints were tested hierarchically at 0.05 (2 sided) according to the sequence in Figure 33. If all the BMD endpoints were significant, the nonvertebral fracture at the primary analysis was evaluated based on a 1-sided test at the significance level determined by the alpha spending function specified in the statistical analysis plan. The adjusted 2-sided p-value was provided to demonstrate the overall significance level of 0.05. All remaining secondary and exploratory efficacy endpoints were explored at significance level of 0.05 (2-sided). If superiority of the nonvertebral fracture endpoint was achieved at the primary analysis and the study was stopped after the primary analysis has been performed, all data, including the additional safety and nonvertebral fracture data, collected after the primary analysis were summarized descriptively.

Figure 32. Summary of Sequential Testing Procedure (Study 337)

Step 1: Subject incidence of new vertebral fracture through month 12 and through month 24 (coprimary endpoints; nominal p-value for each endpoint < 0.05)

↓

Step 2: Subject incidence of clinical fracture through month 12

↓

Step 3: Subject incidence of nonvertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

↓

Step 4: Subject incidence of clinical fracture through month 24

↓

Step 5: Subject incidence of major nonvertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

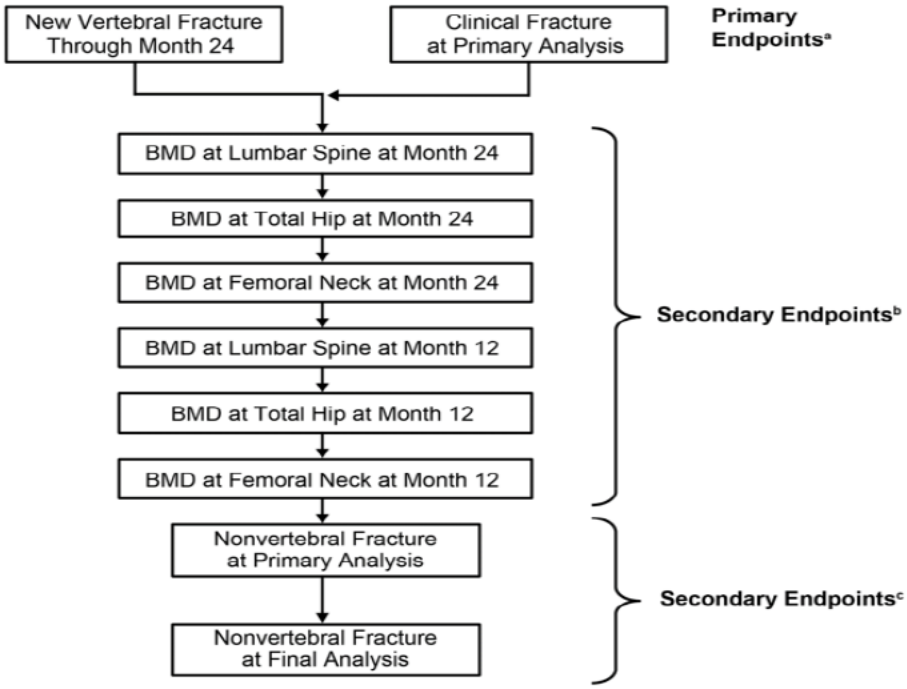
↓

Step 6: Subject incidence of new or worsening vertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

↓

Step 7: Subject incidence of hip fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

Figure 33. Primary and Key Secondary Endpoint Sequential Testing Procedure (Study 142)



[a] Primary endpoints tested at 0.05 level (2-sided), accounting for multiplicity using the Hochberg procedure.
[b] A fixed sequence testing procedure was used for BMD endpoints at the 0.05 level (2-sided) if both the primary endpoints were significant at the 0.05 level (2-sided).
[c] The nonvertebral fracture endpoint was tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test ($\alpha = 0.025$).

Appendix 4. Fatal Adverse Events Occurring in ≥ 2 Subjects in Any Treatment Group by Preferred Term (Pivotal Fracture Studies, 12-Month Double-Blind Period)

	337		142	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
Number of subjects reporting fatal treatment emergent adverse events	24 (0.7)	29 (0.8)	22 (1.1)	30 (1.5)
Death	5 (0.1)	5 (0.1)	2 (<0.1)	1 (<0.1)
Lung neoplasm malignant	0 (0.0)	4 (0.1)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Cardiac failure	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Cardio-respiratory arrest	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)
Myocardial infarction	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Angina pectoris	2 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)
Cerebrovascular accident	2 (<0.1)	0 (0.0)	2 (<0.1)	1 (<0.1)
Pneumonia	0 (0.0)	0 (0.0)	4 (0.2)	1 (<0.1)
Sudden death	1 (<0.1)	0 (0.0)	2 (<0.1)	1 (<0.1)

N = Number of subjects in the analysis set; n = Number of subjects reporting ≥ 1 event; QM = once monthly; QW = weekly
Preferred terms are coded using MedDRA version 20.0.
Alendronate subject (b) (6) in Study 142 had a fatal non-treatment-related serious adverse event of Pneumonia that had an incorrect death flag in the primary analysis snapshot and was not included in the subject incidence of fatal events.
Source: Modified from ISS Table 14r-6.2.9

Appendix 5. Most Frequent Serious Adverse Events (≥ 0.4% of Subjects in Any Treatment Group) by Preferred Term (Pivotal Fracture Studies, 12-Month Double-Blind Period)

	337		142	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
Number of subjects reporting SAEs	**314 (8.8)**	**344 (9.6)**	**278 (13.8)**	**262 (12.8)**
Pneumonia	10 (0.3)	19 (0.5)	17 (0.8)	16 (0.8)
Femur fracture	7 (0.2)	4 (0.1)	12 (0.6)	11 (0.5)
Acute myocardial infarction	4 (0.1)	6 (0.2)	2 (< 0.1)	8 (0.4)
Osteoarthritis	15 (0.4)	6 (0.2)	5 (0.2)	6 (0.3)
Urinary tract infection	7 (0.2)	4 (0.1)	8 (0.4)	8 (0.4)
Chronic obstructive pulmonary disease	15 (0.4)	6 (0.2)	10 (0.5)	5 (0.2)
Radius fracture	5 (0.1)	3 (< 0.1)	12 (0.6)	8 (0.4)
Femoral neck fracture	8 (0.2)	3 (< 0.1)	12 (0.6)	5 (0.2)
Back pain	1 (< 0.1)	2 (< 0.1)	9 (0.4)	2 (< 0.1)

N = Number of subjects in the analysis set; n = Number of subjects reporting ≥ 1 event; QM = once monthly; QW = weekly
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 20.0.
Source: ISS Table 14r-6.2.2

Appendix 6. Key Enrollment Criteria of Phase 2 and Phase 3 Studies

<table>
<tr><th></th><th>Study 337
(phase 3)</th><th>Study 142
(phase 3)</th><th>Study 326
(phase 2a)</th><th>Study 291
(phase 2b)</th><th>Study 156
(phase 3)</th><th>Study 289
(phase 3b)</th></tr>
<tr><td>Comparator(s)</td><td>Placebo</td><td>Alendronate</td><td>Placebo, alendronate, teriparatide</td><td>Placebo</td><td>Placebo</td><td>Teriparatide</td></tr>
<tr><td rowspan="4">Diagnosis and main criteria for eligibility[a]</td><td>postmenopausal women (age ≥ 55 to ≤ 90) with osteoporosis</td><td>postmenopausal women (age ≥ 55 to ≤ 90) with osteoporosis</td><td>postmenopausal women (age ≥ 55 to ≤ 85) with low BMD</td><td>postmenopausal women (age ≥ 55 to ≤ 85) with osteoporosis</td><td>postmenopausal women (age ≥ 55 to ≤ 90) with osteoporosis</td><td>postmenopausal women (age ≥ 55 to ≤ 90) with osteoporosis</td></tr>
<tr><td>no recent treatment for osteoporosis</td><td>no recent treatment for osteoporosis</td><td>no recent treatment for osteoporosis</td><td>no recent treatment for osteoporosis</td><td>no recent treatment for osteoporosis</td><td>bisphosphonate for last 3 years with last year being alendronate</td></tr>
<tr><td>BMD T-score must be ≤ -2.50 at the total hip or femoral neck (lower limit of -3.5 at total hip or femoral neck)</td><td rowspan="2">total hip/femoral neck BMD T-score ≤ -2.50 and history of vertebral fracture (≥ 1 moderate or severe or ≥ 2 mild); OR ≤ -2.00 and history of ≥ 2 moderate or severe vertebral fractures or a recent hip fracture (no lower limit to BMD T-score)</td><td>BMD T-score must be ≤ -2.0 at the lumbar spine, total hip, or femoral neck (lower limit of -3.5)</td><td>BMD T-score must be ≤ -2.50 at the lumbar spine, total hip, or femoral neck (lower limit of -3.5 [-4.0 at lumbar spine])</td><td>BMD T-score must be ≤ -2.50 at the lumbar spine, total hip, or femoral neck (lower limit of -3.5 at total hip or femoral neck)</td><td>BMD T-score must be ≤ -2.50 at the lumbar spine, total hip, or femoral neck (no lower limit)</td></tr>
<tr><td>no history of hip fracture or severe vertebral or more than 2 moderate vertebral fractures</td><td>no history of vertebral fracture or fragility fracture of the wrist, humerus, hip or pelvis after age 50</td><td>no history of vertebral fracture or hip fracture</td><td>must have history of fragility fracture or ≥ 2 clinical risk factors for fracture</td><td>must have history of nonvertebral fracture after age 50 or vertebral fracture at any time</td></tr>
</table>

[a] All enrolled subjects were required to have at least 2 evaluable vertebrae in the L1 to L4 region and 1 evaluable hip.

Appendix 7. Subject Incidences of Positively-Adjudicated CV Death, Myocardial Infarction, and Stroke by DCRI and the TIMI Study Group During the 12-Month Double-Blind Period (Studies 337 and 142)

	DCRI Adjudicated		TIMI Adjudicated	
Study Adverse Event Category	Control n (%)	Romosozumab 210 mg QM n (%)	Control n (%)	Romosozumab 210 mg QM n (%)
Study 337	(N = 3576)	(N = 3581)	(N = 3576)	(N = 3581)
CV death[a]	15 (0.4)	17 (0.5)	12 (0.3)	15 (0.4)
Myocardial Infarction	8 (0.2)	9 (0.3)	8 (0.2)	7 (0.2)
Stroke	10 (0.3)	8 (0.2)	8 (0.2)	8 (0.2)
Study 142	(N = 2014)	(N = 2040)	(N = 2014)	(N = 2040)
CV death[a]	12 (0.6)	17 (0.8)	10 (0.5)	14 (0.7)
Myocardial Infarction	5 (0.2)	16 (0.8)	6 (0.3)	16 (0.8)
Stroke	7 (0.3)	13 (0.6)	5 (0.2)	13 (0.6)

DCRI = Duke Clinical Research Institute; MedDRA = Medical Dictionary for Regulatory Activities;
Control = placebo in Studies 174 and 337 and alendronate 70 mg QW in Study 142.
[a] Death events include fatal events adjudicated as cardiovascular-related or undetermined.
Source: Table 10 and Table 14-6.2.10 of the CV report

Appendix 8. Cardiovascular Safety Subject Disposition (Safety Analysis Set) (DCRI Adjudication of Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
Number of subjects completed double blind period	3198 (89.4)	3190 (89.1)	1820 (90.4)	1833 (89.9)
Number of subjects who discontinued study during double blind period	378 (10.6)	391 (10.9)	194 (9.6)	207 (10.1)
Positively-adjudicated CV event	20 (0.6)	22 (0.6)	20 (1.0)	20 (1.0)
Positively-adjudicated CV death	10 (0.3)	12 (0.3)	10 (0.5)	12 (0.6)
Non-fatal positively-adjudicated CV event	10 (0.3)	10 (0.3)	10 (0.5)	8 (0.4)
No positively-adjudicated CV event	358 (10.0)	369 (10.3)	174 (8.6)	187 (9.2)
Administrative decision	1 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)
Adverse event	38 (1.1)	40 (1.1)	21 (1.0)	22 (1.1)
Consent withdrawn	242 (6.8)	253 (7.1)	117 (5.8)	121 (5.9)
death	7 (0.2)	10 (0.3)	8 (0.4)	10 (0.5)
Ineligibility determined	4 (0.1)	4 (0.1)	2 (<0.1)	2 (<0.1)
Lost to follow-up	21 (0.6)	22 (0.6)	13 (0.6)	13 (0.6)
Noncompliance	17 (0.5)	8 (0.2)	4 (0.2)	7 (0.3)
Other	23 (0.6)	28 (0.8)	5 (0.2)	9 (0.4)
Protocol deviation	3 (<0.1)	2 (<0.1)	2 (<0.1)	3 (0.1)
Protocol specified criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Requirement for alternative therapy	2 (<0.1)	2 (<0.1)	1 (<0.1)	0 (0.0)

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Appendix 8. Cardiovascular Safety Subject Disposition (Safety Analysis Set) (DCRI Adjudication of Studies 337 and 142)

	Study 337		Study 142	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
Number of subjects completed overall study period	2886 (80.7)	2858 (79.8)	1502 (74.6)	1524 (74.7)
Number of subjects discontinued study during overall period	690 (19.3)	723 (20.2)	512 (25.4)	516 (25.3)
Positively-adjudicated CV event	66 (1.8)	65 (1.8)	87 (4.3)	89 (4.4)
Positively-adjudicated CV death	34 (1.0)	34 (0.9)	50 (2.5)	51 (2.5)
Non-fatal positively-adjudicated CV event	32 (0.9)	31 (0.9)	37 (1.8)	38 (1.9)
No positively-adjudicated CV event	624 (17.4)	658 (18.4)	425 (21.1)	427 (20.9)
Administrative decision	13 (0.4)	30 (0.8)	1 (<0.1)	0 (0.0)
Adverse event	57 (1.6)	60 (1.7)	39 (1.9)	39 (1.9)
Consent withdrawn	340 (9.5)	377 (10.5)	250 (12.4)	271 (13.3)
death	32 (0.9)	27 (0.8)	37 (1.8)	37 (1.8)
Ineligibility determined	4 (0.1)	4 (0.1)	2 (<0.1)	2 (<0.1)
Lost to follow-up	55 (1.5)	65 (1.8)	49 (2.4)	38 (1.9)
Noncompliance	50 (1.4)	26 (0.7)	16 (0.8)	15 (0.7)
Other	67 (1.9)	62 (1.7)	20 (1.0)	19 (0.9)
Protocol deviation	4 (0.1)	3 (<0.1)	3 (0.1)	3 (0.1)
Protocol specified criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Requirement for alternative therapy	2 (<0.1)	4 (0.1)	8 (0.4)	3 (0.1)

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N = Number of subjects who received at least one dose of investigational product
Subjects with positively adjudicated cardiovascular serious adverse events are counted as having the event that occurred first.
CV death events include fatal events adjudicated as cardiovascular-related or undetermined.
Source: Table 14z-1.3